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SATURDAY MAY 28 1955

TABLE OF CONTENTS

The Natural History of Anaemia Associated with Protein Malnutrition A. W. WOODRUFF, M.D., Ph.D., F.R.C.P., D.T.M.&H. 1297

Expression of the Sickle-cell Gene in Africa G. M. EDINGTON, M.D., D.C.P., D.T.M.&H., and H. LEHMANN, M.D., Ph.D., F.R.I.C. 1308

Osteomalacia in von Recklinghausen's Neurofibromatosis PAUL D. SAVILLE, M.B., M.R.C.P., J. R. NASSIM, B.M., F.R.C.P., F. HARWOOD STEVENSON, M.D., M.R.C.P., LILY MULLIGAN, B.SC., and MARGARET CAREY, B.SC. 1311

Post-operative Staphylococcal Enterocolitis During Antibiotic Therapy B. J. FOWLER, F.R.C.S. 1313

Repair of Injuries to the Tendons of the Hand R. F. BOGDANOV, M.D. 1315

Incision for Gall-bladder Surgery D. C. CORRY, M.D., F.R.C.S. 1317

Multiple Toxic Effects of Phenylbutazone THOMAS N. FRASER, M.D., F.R.C.P., F.R.F.P.S. 1318

A Case of Stevens–Johnson Syndrome with Extensive Surgical Emphysema HUMPHREY J. A. HAHN, M.B. 1321

Paraplegia Following the Use of "Efocaine" MAURICE J. PARSONAGE, M.B., M.R.C.P., D.C.H., DERYCK TAVERNER, M.D., M.R.C.P., and G. H. WOOLER, M.D., F.R.C.S. 1322

MEDICAL MEMORANDA

Renal Carcinoma. J. BRUCE, F.R.C.S.Ed., and J. G. MACLEOD, M.B., F.R.C.P.Ed. 1323

Bilateral Calcification of the Breasts. F. E. WEALE, M.B., F.R.C.S. 1323

Varicella with Neurological Complications in an Adult. M. S. PATHY, M.R.C.S. 1324

BOOK REVIEWS 1325

REFRESHER COURSE

Post-partum Maternal Collapse. JOSEPHINE BARNES, D.M., F.R.C.S., F.R.C.O.G., M.R.C.P. 1333

GENERAL ARTICLES AND NEWS

Jubilee of Sheffield University 1335

British Association of Physical Medicine 1338

OBITUARY

W. M. Robson, M.D., F.R.C.P. 1344

W. F. Annand, M.D. 1344

T. W. J. Johnson, M.D., F.R.C.P., F.R.A.C.P. 1345

Otto Rosenheim, Ph.D., F.R.S. 1345

J. MacK. Johnstone, M.B. 1346

A. H. B. Heesom, M.R.C.S., L.D.S. 1346

James Scott, M.C., M.B. 1346

Ll. W. Davies, O.B.E., M.D. 1346

C. A. R. McCay, F.R.C.S.I., D.P.H. 1347

R. Davies-Colley, C.M.G., M.Ch., F.R.C.S. 1347

LEADING ARTICLES

Anaemia and Protein Malnutrition 1327

Sterilizing the Gut 1328

ANNOTATIONS

An Epidemiological Centenary 1329

Clinical Thermometers 1330

Tendon Repair 1330

Royal Society Conversazione 1331

Toxic Effects of Cobalt 1331

Cineradiography 1332

Surgery, Gynecology and Obstetrics 1332

CORRESPONDENCE

Diversities of Sex. M. OLDFIELD, F.R.C.S. 1338

Thermometers. G. WESTON, B.SC 1339

SUPPLEMENT

Full Contents on First Page of Supplement

Annual Conference of Representatives of Local Medical Committees 255

Anonymity in Broadcasting. L. J. WITTS, M.D., F.R.C.P. 263

Correspondence:

Part-time Consultants and Income Tax. W. A. BOURNE, M.D. 264

Remuneration of S.H.M.O.s. E. SNELL, L.R.C.P.Ed. 265

Ship Surgeons. D. MCLAREN, M.B. 265

CORRESPONDENCE—*contd.*

Niddah. B. SANDLER, M.D. 1339

Professional Secrecy. R. FORBES, M.B. 1339

Reserpine. D. L. M. MCNEILL, M.R.C.S. 1339

Pesticides. R. H. SCOTT, M.R.C.S. 1340

Idiopathic Pulmonary Haemosiderosis. J. M. CLIFF, M.R.C.P. 1340

Barbiturate Antagonist. J. P. BINGLE, B.M., and J. G. WHITWAM, M.B. 1340

Appendicitis. W. SILBER, M.B. 1341

Hysterectomy. V. B. GREEN-ARMYTAGE, F.R.C.S. 1341

Undergraduate Education in Preventive Health. A. YARROW, M.B. 1341

Changing Face of Medicine. H. D. FORBES FRASER, M.R.C.S.; J. MACLEOD, M.D. 1341

Opportunities for Medical Practice. O. C. FORBES, M.B. 1342

Cancer. F. E. LOEFFLER 1342

Measles. R. A. GOODBODY, M.D. 1343

Chicken-pox. G. E. BREEN, M.D. 1343

Salk Vaccine. J. S. CAMPBELL, M.R.C.S. 1343

Heroin. D. MILWARD, M.B.; R. G. SIMPSON, M.D.; J. H. CRAWFORD, F.F.A. R.C.S. 1343

Food-poisoning. B. H. KIRMAN, M.D. 1343

Adoption. M. E. EDWARDS 1344

British Society of Dental Hypnotists. E. E. WOOKEY, L.D.S. 1344

Vital Statistics 1348

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY MAY 28 1955

THE NATURAL HISTORY OF ANAEMIA ASSOCIATED WITH PROTEIN MALNUTRITION*

BY

A. W. WOODRUFF, M.D., Ph.D., F.R.C.P., D.T.M.&H.

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During the past three decades it has become clear that protein malnutrition is a major cause of death and disability throughout the Tropics. Its severest effects are on infants and young children, but there are reasons for believing that older children and adults, and particularly pregnant women, are affected by it. The term "protein malnutrition" has been discussed by Platt (1953); its meaning is wider than simple dietary protein deficiency, and includes disturbances produced primarily by underfeeding but aggravated by zymotic agents and infection which may convert borderline nutrition into malnutrition.

The study on which these lectures are based began in 1950 in Nigeria when I was confronted with a number of severely anaemic pregnant women. Anaemia in pregnancy is common in Nigeria and throughout the Tropics, and difficulties were encountered in finding an effective remedy for it. Similar difficulties were experienced by Napier (1940) in treating anaemia in pregnancy in India. Earlier work (Woodruff, 1951) has indicated that protein malnutrition plays an important part in the causation of this anaemia, and there is prevalent in Nigeria, as in the Tropics generally, the disease variously known as malignant malnutrition, kwashiorkor, and fatty liver disease. This has recently been referred to as the protein malnutrition syndrome in childhood. It is associated with an anaemia, and, in view of this, further investigations were undertaken to answer the question whether the anaemia in protein malnutrition in childhood is similar to or different from that encountered in pregnant women. There were obvious similarities between both sets of patients in that they were living on poor diets; in the children there was a special demand for protein imposed by the growth of their own body, and in the pregnant women a similar demand imposed by the foetus.

In considering the anaemias associated with protein malnutrition it is necessary to take into account many facts relating to the persons affected, their disease, and their environment. Thus the local foods are of obvious importance; so are the parasites and other causes of locally prevalent diseases, and the habits and social customs of the people.

*Being the text of the Goulstonian Lectures delivered before the Royal College of Physicians of London on February 23 and 25, 1954.

The patients were all studied at hospitals associated with University College, Ibadan, Nigeria, a town which has grown rapidly during the last 50 years and in which the social and economic conditions prevailing have previously been described (Woodruff, 1951).

Although poverty plays a part in the causation of malnutrition, Trowell *et al.* (1954) have drawn attention to the fact that malnutrition often depends more on the type of crops grown in the patients' neighbourhood than on monetary wealth. Thus in a cassava-growing region wealthy people may live on an unbalanced and poor cassava diet. Certainly the parents of grossly malnourished children often are sufficiently well off to wear costly clothing. Taboos are important causes of malnutrition in some regions. Thus in Western Nigeria a common taboo prohibits the eating of eggs, so although hens are numerous no use is made of the valuable source of protein their eggs supply.

Methods of Investigation.—The haematological methods used were standard and have previously been described in detail (Woodruff, 1951). The electrophoretic studies of plasma proteins were made with paper as described by Flynn and de Mayo (1951). Reticulocyte ripening was studied by the method described by Nizet and Robscheit-Robbins (1950).

ANAEMIA AND MALNUTRITION IN PREGNANT WOMEN

These patients, numbering 45, all complained of lassitude and weakness, and many of dyspnoea. Only two gave a history of having had soreness of the tongue. The most outstanding clinical findings were hepatomegaly and splenomegaly. The liver was palpable in 30 and the spleen in 32 cases. In 10 the liver reached 3 in. (7.5 cm.) or more below the costal margin, and the spleen did so in nine. Subcutaneous oedema was present in 10 cases and ascites in one. No evidence of cardiac failure was found to explain the hepatosplenomegaly or oedema. A trace of albumin was present in the urine of several patients, but there were no casts.

The haematological findings for 40 patients are shown in Table I; in the remaining five cases either the patient was first seen in convalescence or full haematological indices were not obtained. It is apparent that these anaemias are of considerable severity; about 50% are normocytic, 25% macrocytic, and 25% microcytic, as judged by the mean corpuscular volume (M.C.V.). The mean corpuscular

TABLE I.—*Haematological Values at Initial Examination in 40 Cases of Anaemia in Pregnancy*

Type of Anaemia	Haemoglobin (g. per 100 ml.)		Red Blood Cells (millions per c.mm.)		M.C.V. (cu.μ)		M.C.H.C. (%)		Reticulocytes (% of R.B.C.)	
	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range
Macrocytic (M.C.V. >95 cu.μ) (11 cases) ..	6·93	5·18–8·70	2·23	1·81–2·90	102·76	95·30–120·40	30·33	26·60–33·30	4·51	1·2– 9·5
Normocytic (M.C.V. 82–95 cu.μ) (19 cases)	5·55	4·62–9·18	2·00	0·89–3·98	86·88	82·30– 93·46	33·04	26·20–38·00	4·49	0·5–16·5
Microcytic (M.C.V. <82 cu.μ) (10 cases) ..	6·66	4·14–9·62	2·60	1·38–3·36	74·26	57·70– 81·81	33·47	28·60–37·68	3·30	0·5– 6·0

haemoglobin concentration (M.C.H.C.) in the majority of cases is satisfactory, and evidence of iron deficiency was infrequent.

Reticulocyte counts at initial examination averaged 4%, indicating that the marrow was active, and this was borne out by microscopical examination of the marrow films, which with two exceptions showed macronormoblastic hyperplasia. In two cases Ehrlich megaloblasts were present. Dr. D. S. Ridley has kindly examined the marrow films and reports that the principal features are: (1) the cells are larger than normal, but not so large as those of the megaloblastic series, the pronormoblasts being 15–21 μ and early normoblasts up to 17 μ in diameter; (2) normal coarsely marked nuclei are found; (3) there is premature haemoglobinization; (4) primitive forms predominate in relation to the scanty late normoblasts; and (5) erythropoiesis is active.

The sickle-cell trait was found in only six cases, thus this abnormality could not be held responsible for the characteristics of the anaemia.

The gastric juice was examined in 39 cases, and histamine-fast achlorhydria was found in 11. Among these 11 patients were the two with megaloblastic marrow.

Schumm's test was positive in 21 cases, so that in these there was a haemolytic process at work. Fairley *et al.* (1938) described such a process in pregnant women suffering from nutritional macrocytic anaemia, and in his cases, too, there was hepatomegaly. Fairley thought it probable that this haemolytic process was initiated by malaria, but continued in the absence of an overt infection. Such a mechanism may be at work in these cases, although haemolytic anaemia in liver disease has been described by Davidson and Fullerton (1938) and by Coleman (1948), and this affords another possible basis for this feature.

In 1950 it was suspected that the anaemia in these cases might respond to liver extract, vitamin B_{12}, or folic acid, for it is associated with a macronormoblastic marrow in which the cells are sometimes difficult to distinguish from megaloblasts. Megaloblastic anaemia in pregnancy has been reported in the Tropics by many workers, and Wills (1931, 1932, 1933), Manson-Bahr (1951), and others have found it to respond to specific haemopoietic substances. Vitamin B_{12} in doses of 100 and 120 μg. failed, however, to bring about a reticulocyte crisis or improvement in the haematological picture. Maximal doses of liver and of folic acid also failed. The therapeutic failure of vitamin B_{12} is understandable in the light of estimations of the vitamin in the serum which Dr. G. I. M. Ross has kindly carried out in five cases, the concentrations ranging from 470 to 1,000 $\mu\mu$g. per ml. The normal range was found by Mollin and Ross (1952) to be from 100 to 720 $\mu\mu$g., with a mean of 358 $\mu\mu$g. per ml. of serum. Thus the values in these women were all normal or slightly above normal.

In macrocytic, normocytic, and microcytic groups iron administered before delivery failed to evoke a reticulocyte crisis or haematological improvement. In one of the cases the M.C.H.C. was as low as 26.6%. Five of the patients improved spontaneously after delivery without treatment. In others, however, this tendency towards spontaneous remission was absent.

The problem, therefore, was of an anaemia often of considerable severity, occurring late in pregnancy, refractory to treatment with iron, folic acid, liver extract, and vitamin B_{12}, and associated with a macronormoblastic marrow and hepatosplenomegaly.

Investigations Concerning the Cause of the Anaemia

Role of Helminths

Of the many questions posed by this anaemia one of the first is whether parasites such as intestinal worms are important aetiological factors. Accordingly stools were searched in all cases; ova of *Ancylostoma duodenale* were found in 14, and ova of *Ascaris lumbricoides* in 34. Treating both worm infections did not, however, influence the anaemia. In many of the cases the infection was light, only very few ova being present. Infection with *A. lumbricoides* is not recognized as a cause of anaemia, though the nutritional demands of this parasite have to be met from the patient's diet and may aggravate any malnutrition present. Infection with *A. duodenale*, where present, no doubt aggravated the anaemia, but the extent to which it did so was probably small, for the characteristics of the anaemia in infected and non-infected persons were similar.

Malaria

One or more blood films from the patients were examined on admission, and subsequently whenever there was fever. Patients found to have overt malaria were excluded from the study. Ibadan is, however, in a highly malarious region, and probably all the patients had been infected in the past but their infections had been adequately dealt with by their immune processes. Malaria may have played a part in the causation of the anaemia and malnutrition, but there is abundant evidence that other very important factors were also at work. Thus patients, and particularly pregnant women, with malarial parasites in the blood and anaemia not uncommonly failed to improve haematologically when given adequate antimalarial treatment.

In well-nourished persons, even when severe anaemia is caused by malaria, the anaemia improves rapidly after adequate antimalarial treatment has been instituted. To one of the pregnant women in this series 600 mg. of mepacrine had been given empirically daily for three days before she was seen for the purpose of this study. Her haemoglobin content was 5.03 g., and her total plasma protein level 5.93 g. per 100 ml. (albumin 1.95 and globulin 3.45 g. per 100 ml.). During the subsequent eight weeks she was delivered, received 2 pints (1.1 litres) of blood by transfusion and 0.9 g. ferrous gluconate daily for three weeks, yet at the end of this period her haemoglobin level was unchanged. She was given a supplement of 4 oz. (113 g.) casein daily, and in two weeks the haemoglobin had risen to 6.2 g., and the total plasma proteins to 7.08 g. per 100 ml. (albumin 3.11 and globulin 3.60 g. per 100 ml.). In cases such as this it is clear that conditions other than malaria are important in preventing recovery from the anaemia.

Significance of the Hepatomegaly

The next question is, what is the significance of the hepatomegaly: is it possible that it is related to the anaemia? Syphilitic disease of the liver was excluded, as the Kahn test, performed in 36 cases, gave a positive result in only one case.

A biopsy of the liver was taken in 42 of the 43 patients, and histological examination showed fatty infiltration in about a quarter of these, and in almost all an increase in fibrous tissue. The fat, when present, was usually in the peripheral portions of the liver lobules, but in some cases it was irregularly distributed; it was never gross, but simulated that seen in mild cases of fatty liver disease in malnutrition of childhood (Woodruff, 1951). The fibrous tissue was

increased in the portal tracts and also occurred diffusely between liver cells. Staining with Wilder's silver method showed that reticulin, instead of being a fine strand between parenchymal cells, was thicker than normal and in multiple strands, often appearing like teased-out rope or lacework. In most cases the cytoplasm of the parenchymal liver cells was thin, vacuolated, and stained badly; in some cells only filaments of cytoplasm were present. Biopsies were repeated after treatment in eight cases, and the late Dr. W. Silvera (who kindly examined the sections) found that in the second specimens the cytoplasm invariably stained better than in the first, and fat where originally present had diminished or disappeared. No change in reticulin was, however, noted. Dr. D. S. Ridley has stained several of these sections for glycogen and found this greatly increased. Certainly the cells are not filled with their normal complement of healthy cytoplasm.

This liver damage has much in common with that found in children suffering from protein malnutrition, and is also similar to that which can be produced in animals by feeding them on diets low in protein and adequate in carbohydrate or fat. Accordingly the question arose whether the anaemia in these cases is the result not of deficiency of a specific haemopoietic factor but of protein, and whether protein malnutrition causes the liver damage and both contribute to the production of anaemia.

Plasma Proteins

The plasma proteins were estimated chemically in 34 cases. The mean values are shown in Table II, from which it will be found that the albumin fraction is reduced and the globulin fraction increased as compared with normal values. Serum was examined electrophoretically in nine cases to determine the type of globulin responsible for the increased amounts present. Typical electrophoretic patterns are shown in Figs. 1 and 2 and may be compared with that from a healthy Syrian woman living in Ibadan (Fig. 3). The mean values of the various protein fractions are summarized in Table III and compared with figures from other patients studied and with those of healthy persons, patients with malaria, and patients with cirrhosis of the liver.

TABLE II.—*Plasma Proteins (g. per 100 ml.) in 34 Cases of Anaemia in Pregnancy*

	Total Protein	Albumin	Globulin	Fibrinogen	A/G Ratio
Mean ..	7·37	3·15	3·76	0·46	0·84/1
Range ..	4·9–8·7	1·9–4·1	2·6–4·9	0·1–1·2	0·48/1–1·48/1
Normal range (Harrison, 1947) ..	5·8–8·8	3·4–6·7	1·2–2·9	0·2–0·4	4·0/1–1·2/1

TABLE III.—*Electrophoretic Separation of Serum Proteins in Cases Studied*

	Albumin (%)	Globulin (%)			
		α_1	α_2	β	γ
Mean of 9 women with anaemia in pregnancy .	38·23	10·60	7·33	10·03	33·81
Mean of 5 young children with severe protein malnutrition	27·89	13·59	15·07	15·99	27·46
Mean of 11 older children, adult males, and non-pregnant females with protein malnutrition and anaemia	25·72	8·99	15·64	12·58	37·07
Normal average: ..					
Ricketts *et al.* (1949) ..	60·30	4·00	9·70	12·80	13·20
Taylor *et al.* (1949) ..	64·10	4·10	7·70	11·40	12·70
Mean of 12 patients with malaria (Taylor *et al.*, 1949)	55·90	6·80	8·10	13·70	15·30
Mean of 7 patients with cirrhosis of liver and ascites (Ricketts *et al.*, 1949)	35·20	4·20	7·20	7·70	35·70

It is clear from a review of the literature on the plasma proteins in malaria (Maegraith, 1948) that in this disease the albumin is reduced and the globulin increased. It is not clear, however, which globulin fraction becomes increased. Taylor *et al.* (1949) infected 12 healthy volunteers with malaria and permitted them to have five to eight paroxysms of fever. The electrophoretic protein patterns before and after the experiment are shown in lines 5 and 6 respectively in Table III. The albumin fraction decreased by 14.5%, the α_1 globulin increased by 62%, and the γ globulin by 19%. Similar changes have been reported by Ganzin (1954).

There is a large literature on the changes in the plasma proteins which may occur in liver disease. The figures given in Table III are those obtained by Ricketts *et al.* (1949) in seven patients with hepatic cirrhosis and ascites, and it is seen that there is nearly three times the normal amount of γ globulin present. The serological changes in the pregnant women fit in most readily with the interpretation that they were brought about by liver damage and to some extent also by malaria.

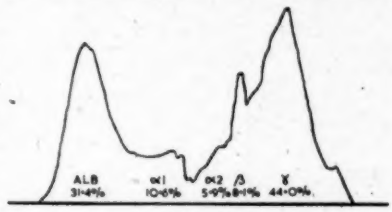


FIG. 1

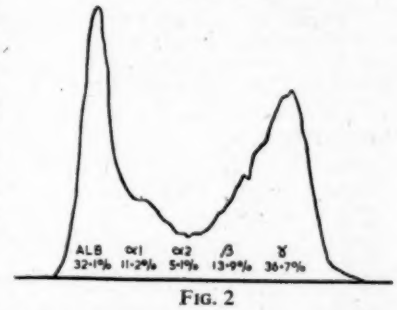


FIG. 2

FIGS. 1 and 2.—Protein pattern obtained by electrophoresis of serum of two of the patients with anaemia in pregnancy. In this and in subsequent similar diagrams figures under Alb. indicate percentage of albumin present, those under α_1, α_2, β, and γ the percentages of the various globulin fractions.

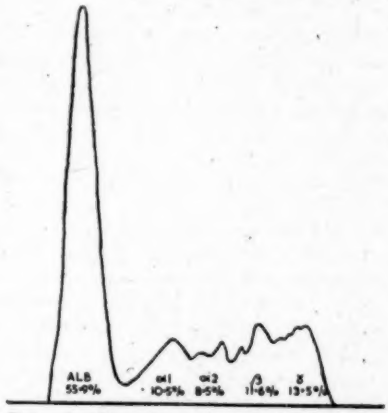


FIG. 3.—Protein pattern obtained by electrophoresis of serum of a healthy Syrian woman living in Ibadan.

The position thus far, therefore, was that these women were anaemic, they were not suffering from deficiency of any known specific haemopoietic factor, and the anaemia appeared not to be caused by the presence of parasites but was associated with liver damage and altered levels of various protein fractions in the blood. The next question which arose was whether there was any evidence that the patients' diets were deficient in protein. Answering this was fortunately facilitated by the fact that the hospitals at Ibadan, like the great majority of those in tropical Africa, do not provide patients with food except in special cases. Food must be brought by relatives or friends, who visit the hospital thrice daily for this purpose. It was thus possible, by weighing and charting the food brought, to obtain an indication of what the patients eat in their homes. In 1950 this was done in 13 cases, and the protein, carbohydrate, and calorie content estimated. The mean daily protein consumption worked out at approximately 50 g., and the total calories provided about 2,000. Miss M. W. Grant, of the Department of Nutrition at the London School of Hygiene and Tropical Medicine, has carefully

checked the diets and these figures, and considers that the values were probably all over-estimated by as much as 30%, the reason being that the water content of the flour used in Ibadan is greater than the figure given in the tables used. Even so, the protein content of the diets was just over half that usually recommended for pregnant women, whereas their calorie value appeared to be adequate. This fitted in with the appearance of the patients, who were fairly well covered. In 1953 more accurate dietary data were obtained, not only by weighing and recording food eaten but by collecting representative samples for analysis. The exact counterpart of food eaten by the patients was placed in a container, aliquots were dried and brought back to this country, and Professor B. S. Platt kindly had these analysed. With the data obtained from these analyses and the records of the patients' diets Miss M. W. Grant and Miss Dare have been able to estimate accurately the calorie, protein, fat, and carbohydrate values of the diets. These are shown in Table IV, and support the suggestion that the

TABLE IV.—*Constituents of the Diet of* 14 *Patients*

Case No.	Calories	Protein (g.)	Fat (g.)	Carbohydrate (g.)
Pregnant women:				
5/53	1,900	56·9	53·3	297·3
6/53	1,303	35·7	59·8	155·2
22/53	1,145	30·0	29·2	190·6
23/53	1,097	43·5	39·3	141·9
27/53	1,439	35·6	56·6	195·6
28/53	1,579	36·7	51·5	241·8
32/53	1,022	26·1	43·2	132·9
34/53	1,112	36·1	34·7	164·7
40/53	1,209	29·5	41·2	179·7
47/53	1,625	33·4	54·6	251·0
Mean	1,343	36·4	46·3	195·1
„ % calories ..	100	10·9	31·0	58·1
Non-pregnant adults:				
29/53	2,740	62·6	77·0	448·3
44/53	976	27·4	32·1	143·6
Adolescents:				
36/53	1,132	30·3	35·2	173·4
48/53	1,432	37·2	45·0	219·3

earlier figures were over-estimates. Thus the mean daily protein intake was 36.4 g. The calorie value was adequate for patients lying in bed.

In the League of Nations *Report on the Physiological Basis of Nutrition* (1936) it is recommended that women between the fourth and ninth months of pregnancy should have 1.5 g. protein per kg. body weight. For the women in this series this would have been 77.3 g. per day. In 1950 the Committee on Nutrition of the British Medical Association recommended that at least 14% of a pregnant woman's calories should be supplied by protein. Thus by either of these standards the women in this series were living on a diet grossly deficient in protein.

A further question which now suggested itself was whether the patients who developed anaemia were those who had an excessive demand on their already poor supplies of dietary protein. This arose from the fact that there seemed to be an extraordinary proportion of twins born of the women studied. Accordingly the obstetric history of the patients was gone into. Much of this has previously been reported (Woodruff, 1951), but, in brief, it has been found that among 45 women studied there was one twin pregnancy in five pregnancies. Ross (1952) states that the ratio throughout the world is 1 in 90. In the United States of America among white persons it is 1 in 88, and among coloured citizens 1 in 67; among Africans in Rhodesia, where Ross was working, the rate is 1 in 35. At Ibadan in 1953 the ratio in 1,000 consecutive hospital deliveries was found to be 1 in 20. Twin pregnancies therefore were four times as common among the anaemic women as they were in non-anaemic pregnant women delivered in hospital at Ibadan. This suggests that those who have heavy nutritional demands imposed by twin pregnancy and are living on this deficient diet are more likely to develop anaemia than are women bearing only one child. The people of Nigeria recognize that to bear twins imposes a greater risk to maternal health than does a single pregnancy, and for this reason have an elaborate ritual following their birth. It is considered that evil spirits are brought by the twins and are responsible for this ill-health. Two wooden idols are therefore made, into which it is hoped the spirits will enter, thus preventing harm to mother or children. As in much folklore, there is some basis for the belief, for certainly anaemia in pregnancy with its associated risks to health is more common among women bearing twins.

Cytological Appearances

There seemed, therefore, to be good evidence that this anaemia was associated with protein malnutrition and with liver damage. Further, this liver damage was of the kind

TABLE V.—*Cell Diameter and Thickness (in μ) in* 34 *Cases of Anaemia in Pregnancy*

Type of Anaemia	M.C.D.		σ		M.C.A.T.	
	Mean	Range	Mean	Range	Mean	Range
Macrocytic (9 cases)	7·87	7·46–8·51	0·76	0·60–0·93	2·07	1·55–2·49
Normocytic (17 cases)	7·61	7·06–8·20	0·90	0·52–2·63	1·94	1·61–2·62
Microcytic (10 cases)	7·52	6·32–8·10	1·06	0·51–2·79	1·76	1·37–2·13
Normal values ..	7·20	6·70–7·70*	0·46	0·40–0·50†	2·10	1·70–2·50‡

* Whitby and Britton (1950). † Larsen (1948). ‡ Price-Jones, Vaughan, and Goddard (1935).

reported by Himsworth (1950) in animals deprived of protein and given adequate calories in the form of fat or carbohydrates—namely, diffuse fibrosis and fatty infiltration. Larsen (1948) found that in patients with acute or chronic liver disease the red blood cells have an increased diameter but diminished thickness. Thus the ratio of their diameter to their thickness is greater than normal. Glynn, Himsworth, and Neuberger (1945) have also reported this type of red blood cell in rats suffering from hepatic disease induced by methionine deficiency. The next question therefore was whether the cells in these cases were also broader and thinner than normal. Their characteristic appearance in thin films suggested that they were. The cells were larger than those of microcytic anaemia, yet they had the pale, vacuolated appearance of those found in that disease. Trowell has called them "foam" or "bubble" cells, and many resemble target cells. There is polychromasia due to the slight increase in reticulocytes and there is also well-marked anisocytosis—a point which is brought out by the wide base of the Price-Jones curves in such cases.

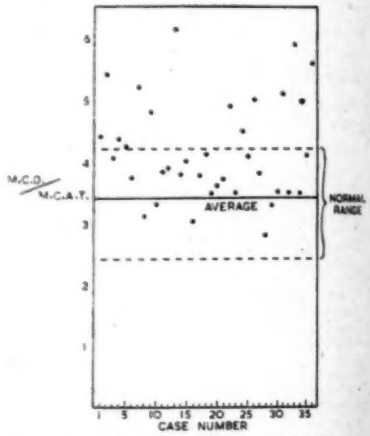


FIG. 4.—The ratio of red blood cell diameter to thickness in 36 women with anaemia in pregnancy. In all but five cases this ratio is greater than the average in health—that is, the cells are thinner than average.

Price-Jones curves were constructed in 36 cases. A shift to the right was present in 24 cases, to the left in only two, and a centrally placed curve was found in 10 cases. In all cases the base was broader than normal. Normal values and the figures obtained from these curves are summarized in Table V. The mean cell diameter (M.C.D.) was increased

even in most cases which were microcytic when classified according to the M.C.V. It was greater than normal in 15 cases, and in the upper half of the normal range in 15 cases. The standard deviation (σ) of the M.C.D., which Larsen (1948) finds is constantly raised in liver disease, was also raised in all cases. The range was 0.51-2.79 μ. The mean corpuscular average thickness (M.C.A.T.) was below normal average in 34 cases. Haden (1935) has shown that normally the diameter of the red blood cell is 2.4–4.2 times its thickness, and that when the diameter is more than 4.2 times the thickness the cell is abnormally thin. The diameter–thickness ratio in the pregnant anaemic women is shown in Fig. 4; it will be seen that in 13 cases the cells were pathologically thin, and in all but five they were thinner than average.

Response to Treatment

In view of the evidence of protein malnutrition, five patients were given daily supplements of 2–4 oz. (56.5–113 g.) casein after a control period of 10 days. This was followed by steady improvement without the development of a well-marked reticulocyte crisis (Fig. 5). In these cases, and in others in which improvement took place on a good diet only, the haematological improvement was invariably accompanied by increase in plasma albumin and by the albumin–globulin ratio becoming less abnormal. In Table VI the values in nine cases before and after treatment are shown and attention is drawn to the fact that albumin has increased in every case.

There is a further important piece of evidence suggesting that protein malnutrition causes liver damage in pregnant women. Following the demonstration of what appeared to be liver damage due to protein malnutrition in anaemic mothers, Silvera and Jelliffe (1952) at Ibadan examined the livers of infants who died within a few hours of being born of malnourished mothers. They found that in several instances the infant's liver was grossly infiltrated with fat and even contained an increased amount of fibrous tissue. This fatty infiltration and fibrosis is of very great interest in that it cannot have been caused by parasites. In two instances vascular or congestive damage arising during childbirth could be excluded by the fact that the two mothers from whose infants the specimens were obtained were delivered by caesarean section. A nutritional cause was the only one likely. It appears that in tropical parts some infants may be born with the handicap of a damaged liver.

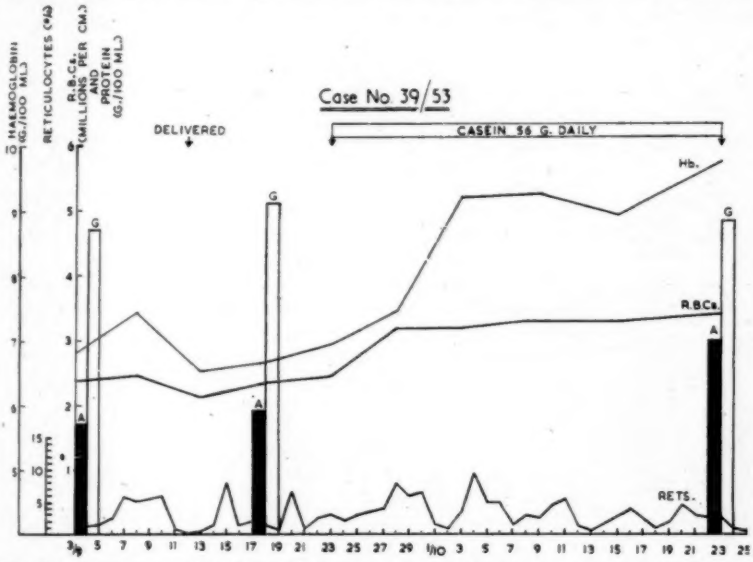


FIG. 5.—Improvement in haematological values in anaemia in pregnancy following treatment with casein. Rectangles labelled A and G indicate albumin and globulin values respectively.

Comment

The evidence thus far therefore suggests that anaemia in pregnant women in Nigeria might be associated with protein malnutrition and liver damage, in some cases no doubt aggravated by parasitic infection. Further, this malnutrition is more likely to develop in those who have heavy demands on their protein supplies. If this hypothesis is correct, then the anaemia of these pregnant women and that of children and non-pregnant adults suffering from protein malnutrition ought to have much in common, and to test the hypothesis a comparison was made of the anaemia in these three types of patients.

ANAEMIA ASSOCIATED WITH PROTEIN MALNUTRITION IN EARLY CHILDHOOD

This series of nine children were studied by courtesy of, and with much help from, Dr. A. Tompkins. All presented with classical clinical manifestations of protein malnutrition or kwashiorkor. They were oedematous, each had a dermatosis and liver damage, and eight had ascites. Their hair, instead of being crisp and curly as it should be in Africans, was soft and straight. One might ask how children are allowed to become so ill, and the answer to that question in part lies in local folklore and superstition. The child affected is commonly believed to be possessed of a spirit or devil, and the advice of an indigenous practitioner is first sought. His usual treatment is to tie the head of a snake, lizard, or rat on to the patient, and it is only when this has failed that help is sought from a hospital or a medically qualified person. Thus we have another example of how ignorance and spurious beliefs play a part in the causation of this disorder.

The age at which this florid clinical condition occurs varies considerably, but the commonest is some months after the cessation of breast-feeding; this takes place much later than in Europe, usually between the ages of 2 and 3 years. At this time the child is given a diet of starchy gruels high in carbohydrate and relatively low in protein. Though the disease is commonest at

TABLE VI.—*Serum Proteins Before and After Treatment in 9 Cases of Anaemia in Pregnancy*

Case No.	Before Treatment					After Treatment				
	Total Protein (g.%)	Albumin (g.%)	Globulin (g.%)	A/G Ratio	Haemoglobin (g.%)	Total Protein (g.%)	Albumin (g.%)	Globulin (g.%)	A/G Ratio	Haemoglobin (g.%)
28/53	5·40	1·95	3·45	0·57/1	3·96	6·71	3·11	3·60	0·86/1	6·22
33/53	6·90	2·22	4·68	0·48/1	5·03	6·26	2·78	3·48	0·80/1	6·96
38·53	6·24	2·62	3·62	0·72/1	4·29	6·63	3·12	3·51	0·89/1	7·25
39/53	6·44	1·70	4·74	0·36/1	6·81	7·75	2·95	4·80	0·62/1	9·77
47/53	6·17	2·31	3·86	0·60/1	7·70	7·10	2·71	4·39	0·62/1	9·18
51/53	7·26	3·18	4·08	0·78/1	6·07	7·73	3·33	4·40	0·74/1	7·55
53/53	6·14	2·47	3·67	0·68/1	5·18	6·12	3·00	3·12	0·96/1	9·18
53/53	5·61	3·00	2·61	1·15/1	7·55	6·00	3·37	2·63	1·28/1	8·58
55/53	7·27	2·84	4·43	0·64/1	4·14	7·60	3·35	4·25	0·79/1	6·66
Mean	6·38	2·47	3·90	0·55/1	5·63	6·88	3·08	3·79	0·84/1	7·93

this age, it may occur in a modified form at any time in childhood, and it seems probable that a variety of it is found in adult life. The ages of the children in this series ranged from 2½ to 6 years. In two of the cases the illness had started after the mother had left the child in the care of a grandparent while she was preoccupied with a later addition to the family. This is not uncommon history, and it is probable that the grandparent, by reason of age or incapacity, is unable to provide more than the cheapest and most readily available foods. These are cassava, yams, and maize, all of which are rich in carbohydrate and poor in protein.

Anorexia was usual, and this is an important symptom as it leads to aggravation of the dietetic deficiency. Oedema, when it first appeared, often affected the most dependent parts of the body, and therefore the side on which the child had been lying during sleep (Fig. 6). Later all the subcutaneous tissue becomes oedematous, and in addition to ascites there may be pleural or pericardial effusions.

FIG. 6.—Unilateral oedema of face following sleep in child suffering from protein malnutrition.

The skin is at first affected in the body flexures, where small folds appear; superficial portions become loose and later drop off, taking with them the pigmented layer. Depigmented patches remain, and soon a condition develops which has been likened to crazy pavement (Fig. 7). It is difficult to avoid the conclusion that most of this shedding of superficial dermis is due to the interference with the nutrition of the superficial layers which results from the oedema beneath pressing on capillaries and restricting blood supply. In addition to this "crazy-pavement" dermatosis, however, there may be generalized dispigmentation of the skin and hair, which, instead of being the normal black of the African child, assumes a light-brown colour. Nagchaudhuri and Platt (1954) have investigated this and found that there are chemical changes in the pigment in the hair of these cases. Such generalized dispigmentation was present in one case.

FIG. 7.—"Crazy-pavement" dermatosis in an African child suffering from protein malnutrition.

In this group of nine children with oedema and skin changes the liver was palpable in seven, the greatest distance below the costal margin being 1½ in. (3.7 cm.). The spleen was palpable in only two cases; in one of these it was just tipped on inspiration, and in the other it was 1 in. (2.5 cm.) below the left costal margin.

Results of Investigations

Haematological Values

Detailed haematological observations were made in six cases. The bone marrow was uniformly macronormoblastic, but megaloblasts were not found and sickling was not detected in any of the six cases.

The haematological indices at initial examination are shown in Table VII. The anaemia, it will be noted, is well marked, though not severe. Schumm's test was negative in all six cases. The M.C.V. is on the low side of the normal range in most cases, but the M.C.D. is abnormally increased in four cases and at the upper limit of the normal range in one case. The M.C.A.T. is below the normal range in all but two cases. There is little evidence of iron deficiency, the lowest M.C.H.C. being 30%. The Price-Jones curves showed a shift to the right in four cases, and in two the curve was centrally placed; in all it was flatter than normal. The standard deviation of the M.C.D. was increased just as it was in the pregnant women, the mean being 0.916 and the range 0.369–1.513. The values for the ratio of cell diameter to thickness in these cases are shown in Fig. 8, from which it is obvious that the cells are very much thinner than normal. This anaemia is therefore orthochromic and, as judged by cell volume, normocytic, but on the basis of cell diameter it is macrocytic. The cells, however, like those of the pregnant women, are thinner than normal and the ratio of cell diameter to cell thickness is increased.

TABLE VII.—*Haematological Values in 6 Children with Protein Malnutrition*

Case No.	Hb (g.%)	R.B.C. (Millions/c.mm.)	M.C.V. (cu.μ)	M.C.H.C. (%)	M.C.D. (μ)	M.C.A.T. (μ)
25/53	6·66	2·07	106·28	30·00	8·82	1·74
30/53	8·88	3·62	71·82	34·15	7·84	1·49
31/53	8·14	3·35	80·59	30·15	8·14	1·55
37/53	8·88	3·21	81·00	34·15	7·84	1·68
42/53	8·58	3·72	69·89	32·61	7·58	1·46
61/53	7·84	2·76	86·96	32·70	7·02	2·24
Mean	8·16	3·12	82·76	32·29	8·04	1·58

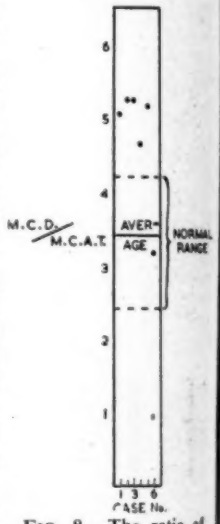


FIG. 8.—The ratio of red blood cell diameter to thickness in six children with anaemia and protein malnutrition. In five cases the cells are pathologically thin.

Parasites

Particular attention has been paid to examination for parasites in these as in all cases in the study. Ova of *A. duodenale* were not found in the stools of any of these children, but in two cases ova of *A. lumbricoides* were found. Blood films were examined for malarial parasites both on admission and subsequently whenever there was fever; in two cases *Plasmodium falciparum* rings were found on admission. Trowell, Davies, and Dean (1952) find that those affected by kwashiorkor usually harbour some parasites, but the same syndrome may occur in the absence of parasitic infections. The findings in this series support this statement.

TABLE VIII.—*Plasma Proteins and Corresponding Haemoglobin Values and Red Blood Cell Counts in 5 Children Suffering from Protein Malnutrition*

Case No.	Date	Total Protein (g.%)	Albumin (g.%)	Globulin (g.%)	Fibrinogen (g.%)	A/G Ratio	Plasma Colloid Osmotic Pressure (mm. Water at 0° C.)	Hb (g.%)	R.B.C. Millions/ c.mm.
30/53	2/9/53	3·85	1·24	2·42	0·19	0·51/1	103·6	8·88	3·62
	29/10/53	7·55	3·88	3·41	0·26	1·14/1	309·4	9·47	3·31
37/53	9/9/53	4·97	0·71	3·96	0·30	0·18/1	115·6	8·88	3·21
	22/10·53	5·94	1·29	4·33	0·32	0·29/1	163·0	10·80	3·94
42/53	26/9/53	4·56	0·91	3·23	0·42	0·28/1	108·2	8·14	3·46
	25/10/53	5·30	1·55	3·70	0·05	0·42/1	154·6	10·66	3·59
31/53 (serum)	29/8/53	4·10	0·20	3·90	—	0·05/1	85·4	8·14	3·35
61/53 (serum)	26/10/53	6·57	3·88	2·69	—	1·44/1	278·0	7·84	2·76
Normal range (Harrison, 1947)		5·8–8·8	3·4–6·7	1·2–2·9	0·20–0·40	4/1–1·2/1	247–342*		

* Keys *et al.*, 1950a.

Plasma Proteins

The plasma proteins were estimated in five of the six cases, and the values obtained, together with the corresponding haemoglobin and red blood cell counts, are shown in Table VIII. In three cases the figures obtained after treatment are also given. By comparison with normal values the albumin fraction before treatment is low and the globulin fraction greater than normal in all but two cases, so that there is a striking inversion of the albumin–globulin ratio. The albumin, it will be noted, increased with treatment. This increase is most marked in the first case, where after eight weeks' treatment with a good diet and a supplement of 56 g. milk protein daily the figures approximated to those at the lower end of the normal range.

The colloid osmotic pressure of the plasma in these cases is shown in Table VIII, the figures for Case 61/53 being obtained during convalescence. These pressures have been calculated from the formula propounded by Keys (1938), who in a series of 40 normal young men found the range to be from 247 to 342 mm. water (Keys *et al.*, 1950a). Thus the values were lower than normal in all four cases in which they were calculated before treatment. The development of oedema is dependent on several factors, of which the plasma colloid osmotic pressure is only one. In nephritis with hypoproteinaemia, Muntwyler *et al.* (1933) found that oedema usually developed when the plasma colloid osmotic pressure dropped below 160 mm. water, and that patients with pressure above this figure had no oedema. His findings accord well with those in this series, in which all the patients had gross oedema and a plasma colloid osmotic pressure below 160 mm. water when first observed. The oedema became less with treatment; when the second reading was obtained, it had disappeared altogether from Case 30/53 and in Cases 37/53 and 42/53 was just perceptible.

Electrophoresis of the Plasma Proteins

In view of the abnormal globulin values found in these children the question again arose as to what globulin fraction predominated. Serum was examined electrophoretically in five cases, a typical curve being shown in Fig. 9; the combined results obtained are shown in Table III and are compared with those in normal serum. Electrophoresis confirmed that in all these malnourished children the albumin fraction was grossly reduced and the α_1 and γ globulin increased. In cirrhosis of the liver the reduction in albumin and increase in β and γ globulins closely parallel the changes in these malnourished children.

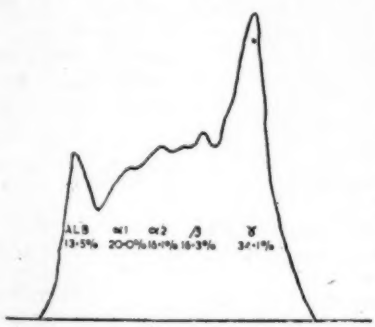


FIG. 9.—Protein pattern obtained by electrophoresis of serum of child with protein malnutrition and anaemia.

In Taylor's malaria experiment (Taylor *et al.*, 1949) the increase in γ globulin was proportionately less, and that of α_1 globulin proportionately greater, than in the children or in cirrhosis. It is of course difficult to compare Taylor's experiment with malaria in volunteers and the findings in these children, who probably had been chronically infected most of their lives. Nevertheless, if the changes were due only to malaria one would expect them to be of the same qualitative kind as in Taylor's experiment. Again, the interpretation which, though provisional, best fits the facts is that the increase in γ globulin is the one that is associated with liver damage and the increase in α_1 globulin is brought about as part of the development of immunity to malaria. Liver damage, malaria, and a low-protein diet probably all contribute to the low albumin values.

Liver Pathology

Liver was obtained for histological examination in all cases. In two this was at necropsy, in the remainder by biopsy. The outstanding features were infiltration with fat and some increase in fibrous tissue in the portal tracts and between the parenchymal cells as in the pregnant women.

Response to Treatment

Regarding treatment in these cases, there is general agreement that best results are obtained with well-balanced diets rich in protein. On admission, therefore, all the patients were given a balanced diet and a 50 g. supplement of casein daily. It was not possible to observe the children during a control period before giving them this diet, as their condition on admission was critical. This was emphasized by the fact that two of them died within a few hours.

The responses of these cases were similar to one another, and in brief this meant a gradual improvement in the clinical condition over a period of weeks or months and a coincident rise in haemoglobin and plasma protein levels. As in the pregnant women, no marked reticulocyte crisis occurred, and this is understandable if there is a deficiency of protein rather than of specific haemopoietic substances. The anaemia would thus be unlike that present in pernicious and similar anaemias, where microquantities of a haemopoietic substance are deficient, the other requirements of haemoglobin production being available. Here it is probable that the materials from which haemoglobin is made are defective or deficient, and this can be corrected only gradually.

The slowness of the therapeutic response in malnutrition and undernutrition has been commented on by many workers. Keys *et al.* (1950b), reviewing the literature on starvation during and after the two world wars, state that the plasma protein level in malnourished persons given a liberal diet increases at only a slow rate. This is understandable on the basis of work done by Elman *et al.* (1942), who from experiments on dogs found that a deficiency of 1 g. of plasma protein is equivalent to one of approximately 30 g. of body protein. Thus by computing the plasma protein deficit and multiplying by 30 a rough indication of the total body protein deficit can be reached. In protein-deficient dogs Elman *et al.* noted that, although infusion of

plasma or amino-acids temporarily raised the plasma protein level, it was only after the total body protein deficit had been replaced that permanent elevation of plasma protein level occurred. On the basis of the plasma protein values and the estimated plasma volume the mean total initial body protein deficit in children in this series can be computed as approximately 450 g. per child. According to the League of Nations (1936) standards the mean daily protein requirement for growth and metabolism of those children worked out at 41 g. It is thus clear that, with these large deficits to make good, a diet containing more than 41 g. of protein daily would be needed for a considerable period before normal plasma protein values could be obtained and maintained.

Reticulocyte Ripening

The rate at which reticulocytes ripened was studied in two children. In the first the estimations were made at an interval of three weeks, during which the haematological values of the plasma proteins had not changed significantly. The rate at which reticulocytes ripened also remained virtually constant, the percentage present in the blood diminishing by increments of 0.5 and 0.6 per hour respectively. In the other case estimations were made at the beginning, in the middle, and at the end of a six-week period, during which the haemoglobin level had risen from 8.88 g. to 10.80 g. per 100 ml., and the plasma protein level from 4.97 g. (albumin 0.71 g.) to 5.94 g. (albumin 1.29 g.) per 100 ml. The successive rates at which reticulocytes ripened also improved, the percentage present in the blood diminishing by increments of 0.5, 0.6, and 1.0 per hour. Similar results were obtained in three pregnant women. In one whose plasma proteins had not changed significantly during three weeks the percentage of reticulocytes present in the blood decreased by 0.4 per hour at the beginning and at the end of the period. In two others whose plasma proteins had respectively improved from 7.45 g. (albumin 2.22 g.) and 6.62 g. (albumin 2.23 g.) to 7.9 g. (albumin 2.80 g.) and 7.53 g. (albumin 2.62 g.) per 100 ml., the rate of reticulocyte ripening also improved. Before treatment the percentage of reticulocytes in the blood decreased by increments of 0.64 and 0.5 per hour respectively, and after treatment in each case by increments of 1% per hour.

Nizet and Robscheit-Robbins (1950) have shown that in dogs with simple anaemia the reticulocytes ripen at the normal rate, but in those with anaemia and hypoproteinaemia ripening is delayed. They found that this delay can be overcome by adding various amino-acids or plasma proteins to the suspension, and conclude that the red blood cell at the reticulocyte stage is able to incorporate plasma proteins into itself or synthesize proteins from amino-acids. Thus if the plasma proteins are abnormal or deficient, some disturbance may take place in the ripening of reticulocytes and therefore in the formation of the mature red cell. These workers state that it is at present not clear whether man is ever subjected to protein depletion severe enough to bring about this effect. The present investigations in children and adults suggest, however, that in protein malnutrition of the kind here being discussed the disturbance is sufficient to delay reticulocyte ripening.

Comment

These children with protein malnutrition therefore have an anaemia. They have histological evidence of liver damage, there is gross abnormality of their plasma proteins with reduction in albumin and increase in globulin, and there is evidence of arrest in the ripening of reticulocytes. The condition responds slowly to a good diet rich in protein.

Thus protein malnutrition and anaemia occur in acute or subacute forms during two phases of life in which growth is rapid: in children when the growth is that of their own body, and in pregnant women when it is that of the foetus. The question arises as to what extent protein malnutrition occurs in association with anaemia at other times of life, and, if it occurs, what are the characteristics of the anaemia.

ANAEMIA AND PROTEIN MALNUTRITION IN OLDER CHILDREN AND ADULTS

Of 21 anaemic older Nigerian children and adults studied, all complained of lassitude, weakness, and inability to carry on with their work; most of them also complained of dyspnoea. In 15 the abdomen was distended by hepatomegaly, splenomegaly, or ascites. In most instances the swelling was of considerable extent, as can be seen from Fig. 10. The liver was palpable in 13 cases and the spleen

FIG. 10

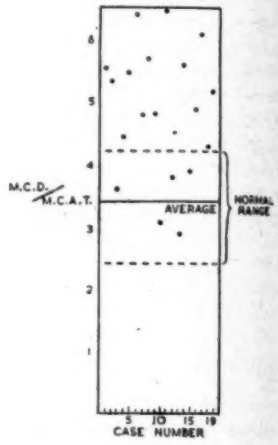


FIG. 11

FIG. 10.—Older child with ascites and cirrhosis of the liver.
FIG. 11.—The ratio of red blood cell diameter to thickness in 19 older children, adult males, and non-pregnant females suffering from anaemia and chronic protein malnutrition.

in eight. The liver was 3 in. (7.6 cm.) or more below the costal margin in four cases; the spleen reached for a similar distance in three. In 11 patients there was ascites, and in 10 clinically detectable oedema. One patient complained of sore tongue. Some fever was present from time to time in most cases, but there were periods of several weeks without any rise in temperature.

TABLE IX.—*Haematological Values in 17 Older Children, Adult Males, and Non-pregnant Females Suffering from Protein Malnutrition*

	Macrocytic (M.C.V. >95 cu.μ) (6 Cases)		Normocytic (M.C.V. 82–95 cu.μ) (2 Cases)		Microcytic (M.C.V. <82 cu.μ) (9 Cases)	
	Mean	Range	Mean	Range	Mean	Range
Hb (g.%)	6·76	2·88– 10·36	8·84	6·07–11·62	7·37	2·66–11·84
R.B.C. (millions/c.mm.)	2·18	1·06– 3·75	3·27	2·14– 4·40	3·40	1·37– 4·59
M.C.V. (cu.μ)	107·84	96·24–131·03	88·98	84·50–93·46	67·94	50·50–78·29
M.C.H.C. (%)	29·37	24·00– 32·66	30·87	30·35–31·40	31·91	28·27–35·39
M.C.D. (μ)	8·22	7·49– 9·75	7·52	7·30– 7·74	7·88	7·13– 8·69
σ	1·37	0·77– 2·10	0·73	0·59– 0·88	0·86	0·66– 1·15
M.C.A.T. (μ)	2·28	2·03– 2·69	1·68	1·35– 2·02	1·46	1·18– 1·82
M.C.D./M.C.A.T.	3·68	2·93– 4·82	4·66	3·61– 5·71	5·44	4·02– 7·34
Reticulocytes (% of R.B.C.)	4·20	0·50– 12·00	0·50	0·50– 1·00	1·56	0·50– 4·00

Results of Investigations

Haematological Findings

The initial haematological values in 17 of these cases are summarized in Table IX; four are excluded as complete haematological investigation was not possible in these cases. Once again the anaemia was well marked, there was no great tendency to hypochromia, the M.C.D. was increased, and the M.C.A.T. diminished in almost all cases. The bone marrow was macronormoblastic, but megaloblasts were not found. Schumm's test was positive in three cases.

The Price-Jones curves were displaced to the right in all but two of the cases, in which they were centrally placed. The curves were broader than normal in all cases. The ratio M.C.D./M.C.A.T. is shown in Fig. 11, and it is apparent that in almost all cases the cells were thinner than normal.

Here, then, were a set of anaemias of considerable severity and almost all associated with hepatosplenomegaly, ascites, or oedema, and a macronormoblastic bone marrow. It was again important to exclude sickle-cell disease and parasites as causes of anaemia, and accordingly appropriate searches were made.

Parasites and the Sickle-cell Trait

Of the 17 cases subjected to detailed haematological studies the sickle-cell trait was present in one-fifth. The characteristics of the anaemia in these cases were similar to those of the others in which the trait was not present, and sicklaemia was accordingly thought not to be an important aetiological factor. Cases of anaemia in which overt malaria were found have been excluded.

Ova of *Ancylostoma duodenale* were found in the stools of eight patients, and ova of *Ascaris lumbricoides* in five, a double infection being present in three. The faeces were free from helminthic ova in seven cases. In a further case the only parasite found was *Taenia saginata*, which can be discounted as a cause of anaemia; in yet another, fatal case a single *A. lumbricoides* was found at necropsy. In most of the cases the infections were light as judged by the number of eggs present in the faeces. It is unlikely that a light infection with *A. lumbricoides* plays an important part in the causation of protein malnutrition or anaemia. If to the three cases in which this parasite alone was present are added the seven without intestinal parasites, and the one infected with *T. saginata* only, it will be seen that in 11 of the 21 cases intestinal parasites could be excluded as a cause of the malnutrition and anaemia. In more than half of the patients, therefore, it seemed unlikely that parasites were playing a part in the causation of the disease at the time of their admission to hospital.

Plasma Proteins

Analysis of the plasma proteins both chemically and electrophoretically gave similar results to those found in the children and pregnant women, the albumin invariably being reduced and the globulin greatly increased. The values in 12 cases are shown in Table X, in which figures obtained before and after treatment are also given. In each of the cases the albumin content improved after treatment with a high-protein diet.

TABLE X.—*Plasma Proteins (g. per 100 ml.) in Older Children, Adult Males, and Non-pregnant Females*

	12 Patients		7 Patients (Means)	
	Means	Range	Before Treatment	After Treatment
Total protein	6·07	3·93–7·30	5·84	6·34
Albumin	1·96	0·62–3·34	1·94	2·49
Globulin	3·82	2·49–5·02	3·64	3·60
Fibrinogen	0·29	0·14–0·50	0·26	0·25
A/G ratio	0·46/1	0·13/1–1·06/1	0·55/1	0·71/1
Haemoglobin	—	—	6·08	7·71

A curve typical of those obtained by electrophoretic separation of the serum proteins in the series is shown in Fig. 12. Mean values estimated electrophoretically in 11 cases are shown in Table III. In these older children and adults the albumin deficit, and the amount of γ globulin present, were greater than in either of the other groups. This and the advanced liver changes found suggested that malnutrition was of longer standing in cases in this group than in the children and pregnant women.

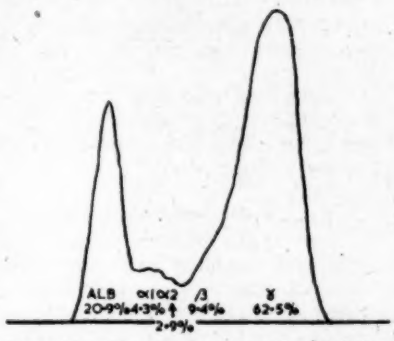


FIG. 12.—Protein pattern obtained by electrophoresis of serum of a child aged 8 years who was oedematous and anaemic.

One point which is clearly brought out by the figures is that the total protein value may give little indication of the disorganization which may be present in the various constituents. Thus one patient's plasma proteins amounted to 7.30 g. per 100 ml., but in that total there was only 1.87 g. albumin compared with 5.02 g. globulin. In an oedematous young male adult who died shortly after admission the figures were: total 5.48 g. (albumin 0.62 g., globulin 4.86 g.) per 100 ml. serum.

Proteins in Ascitic Fluid

The electrophoretic pattern of the proteins in ascitic fluid and the rate at which fluid accumulated were determined in two cases. It was found that in one approximately 4.6 g., and in the other 7.5 g., of protein were being lost into the fluid daily. Thus the onset of ascites in one of these malnourished persons may constitute a serious drain on protein supplies. In one case the rate of production of fluid fell from 200 ml. to 80 ml. daily after the institution of a high-protein diet. No emphasis is placed on this observation in a single case, but it fitted in well with the hypothesis that protein malnutrition was the most important factor in the causation of the ascites.

FIG. 13.—Frozen section of liver from a child who died at the age of 8 with cirrhosis of "hobnail" type. Note fibrous strands and fatty infiltration. The fat appears black in the photograph. (Stain Sudan III and haematoxylin. ×35.)

Liver Histology

Specimens of liver were obtained either by biopsy or at necropsy in all cases. Again, either fat or fibrosis was a constant finding, and in two cases cirrhosis was gross and

advanced. In one child who died at the age of 8 the liver was found at necropsy to be of the typical "hobnail" type, and in addition to being cirrhosed it was also grossly infiltrated with fat (Fig. 13). Such changes are almost certainly later chronic manifestations of the process which is seen in its early acute form in younger children and pregnant women.

One adult male who died had a primary carcinoma of the liver in addition to gross cirrhosis. On the primary nature of this growth the late Dr. W. D. Silvera and Dr. D. S. Ridley were agreed.

Hippuric Acid Excretion Test

In view of the histological and naked-eye evidence of liver damage obtained it is hardly surprising that abnormally small quantities of hippuric acid were excreted after the usual test doses of 6 g. sodium benzoate had been given. In the five cases in which this was done the mean amount of hippuric acid excreted in four hours and expressed as benzoic acid was 0.946 g., range 0.471–1.973 g. Harrison (1947) considers values below 2.5 g. to be abnormal.

Response to Treatment

In this group treatment was even more difficult than in the children or pregnant women. In general the results were poor, but small increases in haemoglobin with coincident improvement in plasma albumin were usually obtainable after the patient had been on a good diet with a supplement of casein for at least two weeks. In those having a treatable infection, such as ankylostomiasis, the outlook was more favourable. The remainder, however, all had advanced chronic liver disease and belonged to a class of patient notoriously unresponsive to treatment. The evidence pointed to the disease in these cases having reached an irreversible stage. Three of the patients died within a few weeks of admission to hospital; all had grossly cirrhosed livers.

DISCUSSION

There is, therefore, evidence that anaemia in some African older children, adult males, and non-pregnant females may be associated with chronic protein malnutrition and liver damage, and this anaemia has the same characteristics as that found in young children and pregnant women. This type of disease is very much more common in the Tropics than in temperate regions. When it occurs it seems to be more chronic than that in children and pregnant women, and unless there are aggravating parasitic factors it is even less amenable to treatment.

Thus protein malnutrition may develop in acute form in childhood and in pregnancy, both periods of rapid growth. It may occur at other times in chronic form if there is a prolonged drain on protein supplies. Some individuals are probably always bordering on this state of malnutrition, and this might be expected to affect their growth and development and to disturb their metabolic and physiological processes. Thus it has been shown by Burke, Harding, and Stuart (1943) that protein deficiency in pregnancy may lead to a low birth weight of the infant. In Nigeria infants born of women with anaemia weigh, on an average, 2 lb. (0.907 kg.) less than those of healthy women (Woodruff, 1954). Platt (1939) has shown that in malnourished children there is a stunting of growth; the growth curves begin to fall away from normal at 6 months of age, and full physical development may never take place. Anaemia and liver damage appear to be other aspects of this malnutrition syndrome.

There is another way in which the disease may manifest itself on a large scale in the Tropics, and this is in the development of gynaecomastia. Several of the male patients in the series suffered from this, and it is a common condition in Africans, Trowell (1948) finding 25 (5%) of 500 East African railway workers so affected. Figs 13 and 14 are photographs of two of the patients

FIG. 14

FIG. 15

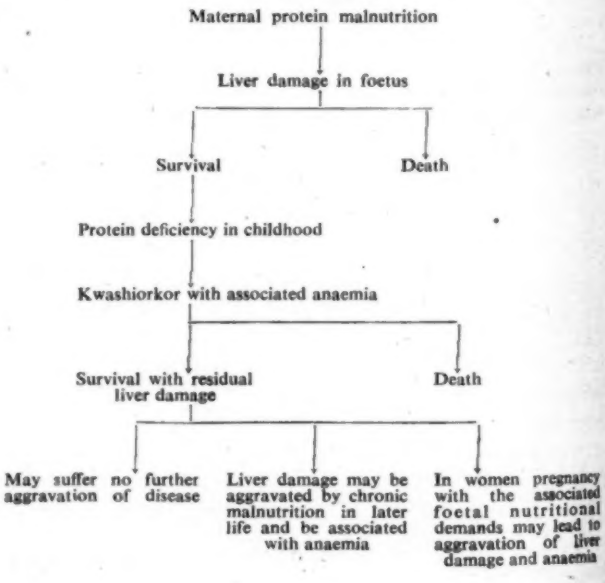
FIGS. 14 and 15.—Gynaecomastia, probably resulting from liver damage caused by protein malnutrition.

studied. In these cases once again liver biopsy showed fatty infiltration or fibrosis. It seems that the gynaecomastia results from damage which renders the liver incapable of inactivating oestrogens normally produced, and this damage also is probably caused by prolonged protein malnutrition. Disturbances of this kind illustrate the gross changes in bodily functions which may occur in the syndrome.

CONCLUSIONS

This study indicates that the natural history of anaemia associated with protein malnutrition may briefly be summed up as follows:

Evolution of Nutritional Macrocytic Anaemia Associated with Liver Damage


Maternal protein malnutrition
Liver damage in foetus
Survival
Death
Protein deficiency in childhood
Kwashiorkor with associated anaemia
Survival with residual liver damage
Death
May suffer no further aggravation of disease
Liver damage may be aggravated by chronic malnutrition in later life and be associated with anaemia
In women pregnancy with the associated foetal nutritional demands may lead to aggravation of liver damage and anaemia

Among certain communities children may be born with livers already damaged by maternal malnutrition. If they survive they again pass through a period following weaning during which the demand for protein imposed by growth is greater than the supply, and the liver is liable to be damaged. At these times an anaemia and other signs of malnutrition may develop. The anaemia is associated with a macronormoblastic marrow and with red cells which are broader and thinner than normal. Many succumb while passing through this stage in childhood; others recover, but probably the majority of these latter are left with some hepatic damage and fibrosis. Nevertheless the functional reserve of the liver is such that, in spite of this, the patient manages until he or she passes through a period in which demands for protein are again in excess of the available supply. In women this state may occur in acute form during pregnancy, foetal growth being the precipitating factor. In adult males and non-pregnant females the disease is less common, but when seen in hospital practice in Nigeria it usually represents a late stage of a chronic process. It develops if the diet is markedly and chronically deficient in protein, and particularly if parasites impose an additional drain on deficient supplies of nutrients. In these cases one of the factors in the causation of the anaemia may be that haemoglobin in its production can draw on plasma proteins, as has been shown by Whipple (1948), and thus when these proteins are abnormal or deficient the production of haemoglobin may be affected. In these cases abnormality, as distinct from deficiency, of plasma proteins may arise from the production of antibodies containing protein, or from liver disease, it being established that the liver plays an important part in protein synthesis.

The characteristics of protein malnutrition in Nigerians are similar whether it occurs in childhood, in pregnancy, or in adult life unassociated with pregnancy. In many cases the disease starts in early life, or even in intrauterine life, and progresses as it is aggravated during periods of growth or deprivation until finally it ends in advanced hepatic cirrhosis with all its concomitant haematological and other features. This stage may even be reached in childhood.

Many of the clinical and pathological states considered in this work are gross and unlikely to be encountered in Great Britain. Nevertheless they provide an insight into the function of various organs and tissues, and into processes which may affect the body in a less florid form in the temperate zones in conditions—such as nephrosis, exudative dermatoses, burns, alcoholism, and cirrhosis of the liver—resulting from non-nutritional causes.

Finally it should be added that Dr. Goulston clearly wished these lectures to illustrate disease processes, for he directed that they should be read "on some dead body, if possibly it can be procured, which shall then and there be dissected for the diseases treated of, and shall afterwards be buried." It is hoped that this study of the natural history of anaemia associated with protein malnutrition may have applications which extend beyond the syndrome seen in the Tropics to disease processes encountered in other regions of the world.

I am grateful for help and co-operation received from many persons while carrying out this work, particularly from Professor A. Brown, Mr. J. B. Lawson, Dr. A. B. Tompkins, and Dr. K. Mellanby. To Professor B. S. Platt I am indebted for much helpful criticism. For technical assistance I wish especially to thank Mr. L. E. Pettitt, Mrs. A. Walshe, and Miss I. Florence. This work would not have been possible without a generous grant from the research funds of the Hospital for Tropical Diseases, London.

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A plea for more enlightened treatment of criminals was made by Sir DAVID HENDERSON in the Morison lecture on "Society and Criminal Conduct," which he delivered last December at the Royal College of Physicians of Edinburgh. He declared that further research must be devoted to the causation and motivation of abnormal conduct. By the time criminal behaviour had been fully established it was often irremediable. The law must be sufficiently elastic to take cognizance of all the data, hereditary, physical, and social, surrounding criminal behaviour. Society must take care that the law is not merely a system of revenge. "We may extol the reformative outlook, but the spirit of revenge and retaliation, of hate and anger, and resentment, has its roots dug deep." His analysis of 150 "lust cases" shows the difficulty of reconciling the legal with the medical approach; a disturbing feature of homosexual cases was the inconsistency of the sentences imposed. Of 129 reprieved murderers, 112 had made a satisfactory readjustment to society. The 150 lust cases showed 81 sane, 17 insane, 26 defective, and 26 psychopathic. Sir David said he had come to believe that abnormality and unsoundness of mind could not be accepted as synonymous. Abnormality demanded an individual approach which could be effected only through clinical research. There was a close parallel between mental illness and the disorders that resulted in crime; both were best treated at a preventive level.

EXPRESSION OF THE SICKLE-CELL GENE IN AFRICA

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It has always been difficult to reconcile the accepted theory of the inheritance of sickle-cell anaemia with the facts found in Africa. Neel (1947, 1949) and Beet (1949) concluded that the sickle-cell gene was harmless in the heterozygote but produced sickle-cell anaemia in homozygotes. Although the sickle-cell trait has been found to be present in 20, 30, and even 40% of individuals in some African peoples, the anaemia is considered to be rare in adults. In infants, however, it has been found to occur with a frequency which falls well within the range of the expected incidence of homozygotes (J. and C. Lambotte-Legrand, 1951 ; Foy, Kondi, and Brass, 1951 ; Vandepitte and Louis, 1953 ; Hutton, 1953 ; Welbourn and Raper, 1954). Nevertheless one of us stated: "I do not believe that in Uganda we could have overlooked sickle-cell anaemia present in all homozygous carriers of the trait. Even if they had died in early infancy, it would have been such a 'slaughter of the innocents' that it could not have escaped our attention" (Lehmann, 1952).

A high incidence of the trait in an adult population with a low incidence of sickle-cell anaemia could be explained most easily by the early death of affected infants. Such a removal of the gene, however, before the age of procreation should lead to a fall in the sickling incidence. Neel (1953) has suggested that the high incidence of the trait found in certain peoples might be explained either (*a*) by a very high rate of mutation from the gene for normal haemoglobin to that for haemoglobin S, sufficient to replace the loss by death from sickle-cell anaemia, or (*b*) by a reproductive advantage over the normal or non-sickling homozygote conferred on the heterozygote by the haemoglobin S gene balancing the disadvantage of the anaemia in S homozygotes—the theory of balanced polymorphism. Neel thought that there was some evidence of an increased mutation rate in his family studies in the U.S.A.; but Vandepitte (1954), in the Belgian Congo, could find no evidence of a mutation rate sufficient to replace the loss of S homozygotes in infancy. Balanced polymorphism has been proposed as a possible mechanism for the maintenance of congenital anaemias by Haldane (1949) and for the survival of the sickle-cell trait by Beet (1946, 1947), by Raper (1949), and particularly by Brain (1952a, 1952b). They all suggested that the sickle cell might be more resistant to tropical parasites, particularly the malaria parasite.

Allison (1954) was the first to report very striking differences in the degree of incidence of malaria parasites in sicklers and non-sicklers, though his work has been challenged by Moore, Brass, and Foy (1954). Recently Raper (1954) has reported a statistically significant difference in the degree of parasitaemia of sickling and non-sickling children during the second year of life.

There exists, however, yet a third possible explanation of the high incidence of the S gene which can be added to those described. If it was found that some healthy African adults were homozygous for the S gene, it would explain in part why sickle-cell anaemia is not found with the expected frequency in adults and why the trait is inherited more often than one would expect if all the homozygotes died in early infancy. One of us (Edington, 1953) was struck by the histories given by patients suffering from sickle-cell anaemia in the Gold Coast. Symptomatically these patients improved with advancing years. One patient aged 44 had been free from crises for nine years and had had six children, three of whom were alive and well ; another, aged 39, was suffering from sickle-cell anaemia but had five children who were all alive and well. In view of the discovery, however, of modified sickle-cell anaemia in individuals heterozygous for S and another inherited abnormality of haemoglobin (sickle-cell–thalassaemia, sickle-cell–haemoglobin C disease, sickle-cell–haemoglobin D disease ; see Itano, 1953a) there was a possibility that these patients were not the true S homozygotes, as electrophoretic analyses of the haemoglobins had not been performed.

Electrophoretic Tests

Until recently the study of the genetics of sickling depended on the testing of whole families for the presence or absence of the sickling character in the red cells and on the clinical condition of those showing sickling ; the diagnosis of homozygosity and heterozygosity was subject to considerable doubt. With the introduction of electrophoretic tests on haemoglobin there is now no reasonable doubt that, subject to certain rare exceptions, a determination of the genotype can be made by means of a single test on the blood of an individual, and need not depend on a study of the rest of the family. Normal non-sickling persons show as a rule 100% of haemoglobin A, and in any case no haemoglobin S. Heterozygous sicklers have both types of haemoglobin, while homozygous sicklers have mainly haemoglobin S, together usually with a varying amount of persistent foetal haemoglobin (haemoglobin F) but no haemoglobin A.

There is very strong evidence that genes for haemoglobins A, C, D, E and G, and S belong to a series of multiple alleles, so that all homozygotes and all heterozygous combinations of them can be diagnosed electrophoretically, except that haemoglobins D and S are indistinguishable, as they have the same electrophoretic mobility. Homozygous haemoglobin D (never yet found) could certainly be distinguished by the absence of sickling, but SS and SD can be separated only by solubility measurements. Haemoglobin S is much less soluble in the reduced state than haemoglobin D ; thus SS and SD can be separated by their different solubilities. To establish the claim that an individual is a homozygote for haemoglobin S, electrophoretic and solubility studies are therefore necessary. As S homozygotes also possess foetal haemoglobin, a possibility arises that individuals with sickle-cell–thalassaemia disease (SAF) could be mistaken for S homozygotes (SSF).

As Itano (1953a, 1953b) has pointed out, the solubility of the haemoglobin of an SS individual depends on the proportion of F being present ; thus the solubility of haemoglobin from an S homozygote with a high proportion of persistent F may be within the same range as the solubility of the haemoglobin of a patient with sickle-cell–thalassaemia disease, in whom the proportion of S is high and that of F moderate and A low. If the amount of A is small—up to 8.2%—it may escape detection by electrophoresis (Singer and Fisher, 1953). Thus a sickle-cell homozygote with a high percentage of foetal haemoglobin and a sickle-cell-thalassaemia individual may not be differentiated by electrophoresis (though this will be exceptional), and the solubility of the two haemoglobin mixtures may be within the same

range, the upper range for that seen in SS homozygotes. If such a finding is made the only recourse is still the family study. However, thalassaemia has never been found in the Gold Coast, in spite of an exhaustive search. This was stimulated particularly by a high incidence of target cells (Edington, 1953).

We have recently conducted a survey of Gold Coast Africans for abnormal haemoglobins (Edington and Lehmann, 1954), and were particularly interested in trying to discover whether in such an investigation symptomless homozygotes for the S haemoglobin could be found. Of the 200 individuals examined, 38 were sicklers, and two of these were homozygous for the S gene (which incidentally would be the expected incidence for homozygotes).

Case 1

J. A. S., a plethoric African man of the Gã tribe aged 40, reported to the out-patient department of the Gold Coast Hospital complaining of epigastric pain occurring about half an hour after meals during the last six weeks. Previous history, family history, physical examination, and laboratory and radiological investigations revealed no abnormality apart from sickling of the erythrocytes and that the patient was symptomatically relieved by alkalis. He had had three children, one of whom, a son aged 22, was alive and well. A boy aged 14 had died of dysentery and a girl aged 7 of "measles." When the analysis of the haemoglobin revealed that J. A. S. was an S homozygote further investigations were made. On direct questioning he admitted that he had suffered from "rheumatism" in childhood. At the age of 8 he had had attacks of pain in the larger joints of the limbs accompanied by fever; these attacks occurred about ten times in that year and gradually lessened in frequency and severity until they ceased at the age of 18.

Laboratory Investigations.—Urine: no sugar, bile, albumin, casts, or urobilin. Kahn test negative; van den Bergh negative; serum bilirubin, 0.3 mg. per 100 ml.; haemoglobin (Grey wedge), 13 g. per 100 ml.; red cells, 4,600,000; reticulocytes, 1.2%; white cells, 5,400; P.C.V., 43%; sickling of the erythrocytes—no filamentous forms noted; thin film and differential count revealed no abnormality apart from the presence of scanty target cells (less than 4%).

Case 2

E. B. A. D., a well-built man of the Akwapim tribe aged 30, reported to the out-patient department of the Gold Coast Hospital complaining of a "rash." He was suffering from a mild neurodermatitis which cleared rapidly with treatment. Analysis of the haemoglobin revealed that he was an S homozygote.

On direct questioning he admitted that he had suffered from attacks of pain in the larger joints which had begun at the age of 12 and were worse in the rainy season. During these attacks his eyes were yellowish and his urine was highly coloured. The attacks were never severe, and ceased at the age of 25, when he stopped playing football—to which game he attributed the illness. His parents were dead, cause unknown. He is married with one child alive and well. Physical examination revealed no abnormality. Neither the liver nor the spleen was palpable.

Laboratory Investigations.—Kahn test negative; serum bilirubin, 0.7 mg. per 100 ml.; haemoglobin (Grey wedge) 15.5 g. per 100 ml.; red cells, 4,860,000; reticulocytes, 1%; white cells, 4,600; P.C.V., 48%; no abnormality detected in the thin film. Urine: urobilin present in a dilution of 1:2.

Investigation of the Haemoglobins

The chemical investigation of the two bloods showed all the features usually considered typical of sickle-cell anaemia. Fig. 1 shows the electrophoretic pattern of the haemoglobin of both individuals—a single band in the S position. Both bloods contained foetal haemoglobin determined by alkali denaturation (Singer, Chernoff, and Singer, 1951). The

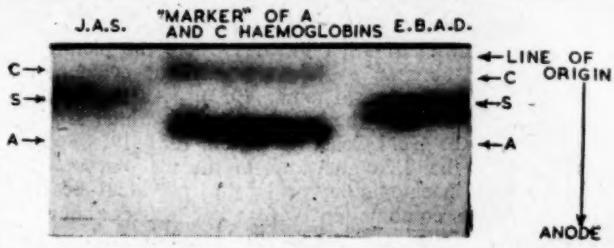

FIG. 1.—The blood of J. A. S. and E. B. A. D., two Gold Coast Africans, is compared by paper electrophoresis with a blood containing as a "marker" A–C haemoglobins. Both individuals show a single band in the S position. Foetal haemoglobin was found by chemical means, but it does not separate on paper electrophoresis from A or S haemoglobin. The haemoglobins are photographed unstained (for detailed technique see Lehmann and Smith, 1954).

solubility of the haemoglobins determined after Itano (1953b) certainly for the first individual fell well within the range of the solubilities found by that author only in sickle-cell anaemia (<0.44 g./l. of 2.24 *M* phosphate buffer).

	% Alkali-resistant (Foetal) Haemoglobin	Solubility in g./l. of 2·24 *M* Phosphate Buffer
J. A. S.	5·2	0·15
E. B. A. D.	24·2	0·50

The second individual shows a high foetal haemoglobin and the solubility is within the range for that seen in both sickle-cell anaemia and sickle-cell–thalassaemia disease (0.44–0.90 g./l. of 2.24 *M* phosphate buffer). It has already been pointed out that the possibility of finding the sickle-cell–thalassaemia disease in the Gold Coast can be disregarded, and so far as the major argument of this communication is concerned it may be stated that from the accepted point of view both sickle-cell homozygotes (SSF) and sickle-cell–thalassaemia individuals (SAF) should be suffering from anaemia.

It thus seems that, at least in the Gold Coast, the homozygous inheritance of the S gene can be a benign condition which would be missed in ordinary clinical and haematological investigations and which may be detected only by the analysis of the haemoglobin.

The Sickle-cell Trait

While it has been shown that every sickle-cell haemoglobin homozygote need not suffer from a severe disease, it cannot, on the other hand, be taken for granted that the heterozygous condition will always be entirely harmless and express itself solely as a trait rather than as a disease. Haematuria due to pathological lesions in the kidney and ascribed to the presence of the sickle-cell trait has been described in American negroes (Harrison and Harrison, 1952). Vernier (1955) summarizes 35 reports of one-sided renal haemorrhage in sickle cell individuals, most of them sickle cell trait carriers.

We have recently seen in Accra a girl of the Gã tribe, aged 18, suffering from haematuria, whose haemoglobin on electrophoretic analysis revealed the presence of the trait—that is, of both normal and sickle-cell haemoglobin. No history of previous illness was given and the physical examination revealed no abnormality. The results of the laboratory investigations were as follows. Urine: numerous red blood cells present; a few of them were abnormally shaped, but no definite sickle cells were seen. Culture was sterile and guinea-pig inoculation was negative. Serum bilirubin, 1.2 mg. per 100 ml.; direct van den Bergh test negative. Hb, 12.3 g. per 100 ml.; red cells, 4,320,000, reticulocytes, 2.8%; white cells, 8,100; P.C.V., 33%; sickling positive. A peripheral blood film showed many target cells with an occasional poikilocyte and polychromatic red cell. The alkaline phosphatase and thymol turbidity were within normal limits. The haematuria cleared within a few days, but no follow-up was possible. It cannot be claimed that the presence of the trait was definitely responsible for this girl's symptoms, but in view of the reports in the American literature it must be considered in the differential diagnosis of the condition.

The sickling phenomenon may certainly play a part in the terminal phases of other diseases where the picture of the crises can be seen at necropsy without evidence of previous acute episodes (Thoma, 1953). At the present moment it is not clear whether these crises, which are not uncommon in the Gold Coast (Edington, 1951, 1955), occur most often in the S homozygote, in the heterozygote for S and normal haemoglobin, or in the individual bearing the S gene in combination with some other abnormal haemoglobin. In an attempt to elucidate this problem we have recently begun to examine electrophoretically the blood of all subjects coming to necropsy, and the crisis has been noted in one woman suffering from sickle-cell haemoglobin C disease. In addition, however, the blood of another woman (K. L.), who presented at necropsy the typical features of the crisis, revealed on electrophoretic analysis the presence of the trait only (normal and sickle-cell haemoglobin) (Fig. 2), as is described in detail below.

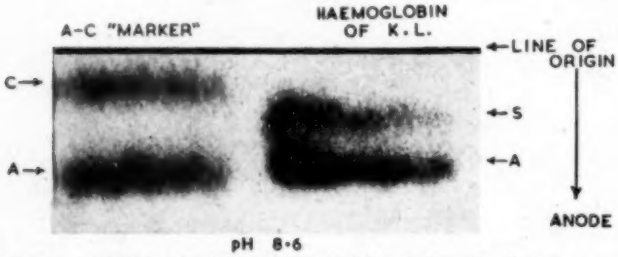

FIG. 2.—The blood of K. L., who died in sickle-cell crisis, is compared by filter-paper electrophoresis (for details see Lehmann and Smith, 1954) with a "marker" blood from an individual heterozygous for A and C haemoglobins. The haemoglobin of K.L. shows bands in the S and A position. K. L. is heterozygous for A and S haemoglobins.

Crisis in a "Sickle-cell-trait Carrier"

K. L., an African woman of the Gã tribe aged 23, was admitted to the Maternity Hospital, Accra, in a comatose condition. Shortly after admission she died following the expulsion of a hydatidiform mole. She had had one previous child, who had died in infancy. No history of previous illnesses was obtained from the relatives. The patient had been ill for two weeks with fever. Substernal pain and cough had been noted during the last week and she was thought to be three months pregnant.

Necropsy Report.—The body was that of a well-built plethoric African female. The sclerae were slightly jaundiced. There was frothy mucus in the trachea and the lungs were congested and grossly oedematous (795 g.). Heart: the left ventricle was hypertrophied; no lesions of the myocardium, valves, or coronary arteries were noted (320 g.). The liver was congested (1,975 g.). The spleen was enlarged, rubbery in consistency, and dark blue in colour (495 g.). The cut surface was dark red and did not bleed on section. The uterus was enlarged to the size of a three-months pregnancy. No abnormal blood clot was present and the placental site appeared macroscopically normal. The remaining abdominal organs exhibited intense pallor and the kidneys were oedematous. The sternal marrow was dark red and dry. The brain was pale and the vessels contained watery blood. The heart's blood showed sickling on direct examination, and electrophoretic analysis of the haemoglobin revealed the presence of sickle and normal adult haemoglobins (Fig. 2).

Histological Examination.—All organs were fixed in 10% formol saline and transferred to formol sublimate saline before embedding. *Liver:* The sinusoids were congested and contained numerous white blood cells; the Kupffer cells were distended and contained numerous sickled erythrocytes; free iron-containing pigment was present in the Kupffer cells and periportal parenchymal cells. Haemofuchsin was not detected; a little malarial pigment was present. *Spleen:* There was gross congestion and haemorrhage and the sinuses were stuffed with sickled cells; the Malpighian corpuscles were widely separated and compressed; the germinal centres were hypertrophied and surrounded by a narrow rim of lymphocytes; traces of free iron-containing pigment were present; a reticulin stain showed interruption of the normal reticulin pattern in the areas of haemorrhage. *Uterus:* Tags of placenta were adherent and a marked polymorphonuclear infiltration with small abscesses was present. *Lung:* The smaller vessels were congested with sickled erythrocytes. The alveoli showed gross oedema and heart failure cells were present. *Kidney:* An occasional hyalinized glomerulus was noted, and there were occasional casts in the collecting tubules. Thrombosed vessels were not noted and no free iron was present. Apart from a normoblastic hyperplasia seen in the sternal marrow no other abnormality was noted in the remaining organs.

Comment.—The gross pathology of the spleen and the histopathology of the liver and spleen were those found in the sickle-cell crisis. Mild haemolysis was also probably present, as shown by the presence of jaundice, iron pigment in the Kupffer cells, and a normoblastic hyperplasia of the sternal marrow. This was probably not of long standing, as there was only a little free iron in the spleen, and none in the kidney. Undoubtedly a septicaemic element was also present, and it is difficult to decide what part this played as an eventual cause of death. It is considered that the terminal crisis was probably initiated by the septicaemic condition and was directly responsible for death.

Discussion

Two Gold Coast Africans, to all intents and purposes healthy, have been found to be homozygous for the sickle-cell gene. Previously it had been thought that most patients suffering from sickle-cell anaemia died in childhood, and it was difficult to explain the high incidence of the trait in certain communities because of this belief. At the present time the mortality occurring in S homozygotes is not known, but it is possible that a considerable number reach adult life, procreate, and lead relatively normal lives. One of us (G. M. E.) has now observed over 50 patients suffering from sickle-cell anaemia, and the prognosis, in the Gold Coast at least, is by no means gloomy. Many of these patients have improved with the passing years and are able to lead useful and normal lives. It is too early yet to venture an opinion on the fertility of these patients, as the majority were children when first seen and have not yet reached the age of marriage, but from the histories obtained in the older patients it is not expected that fertility would be greatly impaired. The survival of the relatively healthy homozygote may be a potent factor in maintaining a high incidence of the trait in certain peoples.

On the other hand, there is no doubt that sickle-cell anaemia is the cause of considerable mortality, the exact extent of which is unknown, and in this communication it has been suggested that the trait itself may be by no means harmless. It is impossible to say to what extent procreation by S homozygotes helps to balance the mortality caused by the sickling phenomenon, but this possibility must be taken into account, in addition to the possible protection afforded by the trait against malaria and a possible high mutation rate of the S gene, when discussing reasons for the persistent high incidence of the trait in certain African and Indian peoples.

Summary

Of 200 individuals examined in the Gold Coast, 19% showed sickling and two (1%) were found to be homozygous for S haemoglobin. They were adults not suffering from sickle-cell anaemia, yet chemically their haemoglobin was indistinguishable from that of such patients.

A sickle-cell crisis is described in a woman heterozygous for sickle-cell and normal haemoglobin.

These findings, and their bearing on the current theories on the expression of the sickle-cell gene and its population dynamics, are discussed.

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OSTEOMALACIA IN VON RECKLINGHAUSEN'S NEUROFIBROMATOSIS

METABOLIC STUDY OF A CASE

BY

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Von Recklinghausen's neurofibromatosis is a hereditary and familial disease. It is characterized by lesions of skin, nerve, and bone. Skeletal abnormalities are said to occur in 7% of cases (Gould, 1918; Reuben, 1934). The commonest abnormality is scoliosis (Hagelstam, 1946; Fairbank, 1951). There may be overgrowth or undergrowth of individual bones, while neurofibromata may erode the bones from the periosteum or cystic changes may occur in bone.

Apart from neurofibromatous affection of bone, the occurrence of osteomalacia in association with neurofibromatosis has been reported too often to be a chance finding. Gould (1918) reported typical histological findings of osteomalacia in five cases of von Recklinghausen's disease which he examined *post mortem*. He gave no indication of the aetiology. Since then further cases have been reported but without full metabolic investigations. Merklen and Israel (1934) described a case of von Recklinghausen's disease with general rarefaction of bone and Milkman's syndrome. Milkman's syndrome is now generally believed to be invariably due to osteomalacia. Nørgaard (1937) described many radiological abnormalities of the skeleton in two cases. In Fig. 3, Case 1, of his article it can be seen that the *x*-ray film of the pelvis shows a pseudo-fracture through the left inferior pubic ramus and another through the superior pubic ramus. The patient was 22 years old, and an *x*-ray film one year previously showed no pseudo-fracture. This patient then was undoubtedly suffering from osteomalacia. Hernberg and Edgren (1949) reported the case of a woman aged 32 with neurofibromata of skin and multiple pseudo-fractures (Looser–Milkman syndrome). She had a serum inorganic phosphorus of only 2 mg. per 100 ml. with normal calcium, and was given 11 million units of vitamin D in twelve weeks with no apparent effect until eight months later, when healing occurred. They suggested that this might be a "parallel phenomenon" to von Recklinghausen's disease or raised resistance to vitamin D. Since then knowledge of the pathogenesis of osteomalacia and rickets has advanced, and it is now clear that these cases are due to a hereditary abnormality of the renal tubule. Dent (1952) described two cases of osteomalacia in von Recklinghausen's disease which he considered to be due to resistant rickets (Types I and II respectively). Fraser and Nordin (1953) reported a case which they felt was due to resistant rickets. Swann (1954) also reported several cases of this syndrome.

We are recording a further case in which the opportunity was taken to make metabolic studies on varying doses of vitamin D, proving conclusively that this disease falls into the group known as resistant rickets. In addition, biopsies were made from affected bone, and the results of these are also reported.

Case History

The patient was a man aged 55 who for seven months before admission had increasingly severe backache, made worse by coughing and sneezing. More recently he noticed aching pain in his shoulders, left ankle, and left foot. Walking was almost impossible. His general health was satisfactory, but he had always had a "weak bladder" and passed urine every 1½ hours by day, and two or three times at night. He had had no relevant past illnesses, apart from "fits" as a child. His father and paternal grandmother had had neurofibromatosis.

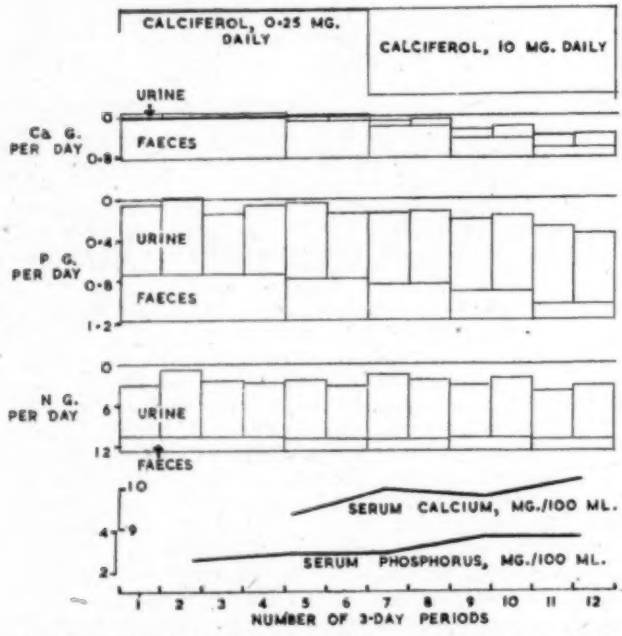
Examination revealed a stunted little man with typical skin lesions, both pigmentation and tumours, covering the trunk, head, neck, and limbs. The right leg was 1½ in. (3.8 cm.) shorter than the left, and all the muscles below the right knee were partially atrophied. There was a tarsal equinocavus deformity of the right foot. He gave the impression of being of rather low intelligence, and was virtually illiterate.

Investigations.—Haemoglobin, 98% (14.5 g. per 100 ml.); W.B.C., 6,750 (normal differential count); E.S.R., 3 mm. (Wintrobe). Urine: normal cytology; sterile on culture, no albumin or sugar. Serum calcium, 9.9 mg. per 100 ml.; phosphorus, 2.2 mg. per 100 ml.; alkaline phosphatase, 14.5 King–Armstrong units; potassium, 5.3 mEq/l.; alkali reserve, 29 mEq/l.; blood urea, 37 mg. per 100 ml.; plasma protein, total 6.9 g. per 100 ml. (albumin 3.2 g., globulin 3.7 g.). Urea clearance, 63% of normal (uncorrected). Glucose-tolerance test, normal, rising from 70 to a maximum of 151 and back to 70 mg. per 100 ml. in two hours. Sugar appeared in the urine at the height of the curve. Paper chromatography of urine: No aminoaciduria; superglycine pattern present, which we have come to associate with osteomalacia in the adult (C. E. Dent). *X*-ray examination showed multiple fractures of ribs ("There is an opacity in the right lower zone which on lateral view is seen to be below the diaphragm, which is tented up over it.") There was some kyphosis and some demineralization of the

spine. "The tibiae and fibulae are markedly porotic. There is a cystic appearance at the upper and lower ends of the left fibula and the upper ends of the tibiae. There is a pseudarthrosis at the lower end of the left fibula, resulting in valgus deformity of the ankle. There are pseudofractures through the lower third of the shaft of the left tibia and neck of right femur." Fat balance: On 80 g. intake there was 93% absorption over twelve days. The patient required four daily doses of 700 mg. of ascorbic acid orally before he was "saturated."

Pathological Report.—Biopsy specimens were taken from the left femur and left fibula, including the pseudarthrosis, and also a chip from the tibia in the region of the pseudofracture, three months after treatment. *Resected portion of fibula:* The specimen consisted of a length of fibular shaft approximately 2 in. (5 cm.) in length. The upper part was reasonably normal in its external appearance, while the lower part was irregular in contour and ended as one surface of a pseudarthrosis. Histologically the lower part of the bone was extremely osteoporotic, and its periosteal surface was deeply indented by irregular masses of mucoid fibrous tissue. Degenerated cartilage and fibrocartilage covered the surface of pseudarthrosis. The upper part of the bone was slightly osteoporotic: excessive amounts of osteoid tissue could not be demonstrated in either situation. *Biopsy from tibia:* Sections showed that the localized rarefaction evident clinically at the site of biopsy (an "Umbauzone" of Looser) was the result of resorption of bone. Haversian spaces were greatly enlarged: there was some irregular new formation of bone, including some periosteal new bone. There was no evidence of excessive amounts of osteoid tissue on the surface of either the compact or the trabecular bone.

Metabolic Procedure.—The patient was admitted to the metabolic ward at the country branch of the Royal National Orthopaedic Hospital. He was not confined to bed, but allowed to sit in a chair. The metabolic regime and the collection of excreta followed the methods advocated by Albright and Reifenstein (1948). Urine was collected in three-day and faeces in six-day periods. Food was prepared by the dietitian in the metabolic unit kitchen. Bulk supplies of meat, biscuits, and homogenized milk were used. Bread was made in the unit from unfortified flour.



In these metabolic charts the intakes are measured vertically downwards from the baseline marked O. Positive balance is indicated by the fact that the rectangles showing urinary and faecal output fall below this baseline—that is, excretion is less than intake; and negative balance when they reach above the baseline—that is, excretion is greater than intake.

Distilled water was used throughout. The diet was analysed twice during the balance. The patient was on this diet eight days before balance studies were recorded.

The diet contained; calcium, 813 mg. per day; phosphorus, 1,184 mg.; nitrogen, 12.55 g. Three litres of distilled water was given daily. Balance data for calcium, phosphorus, and nitrogen for six consecutive six-day periods are shown in the Chart. The following points will be noted:

Six-day Periods 1–3.—Patient was given 0.25 mg. (10,000 units) calciferol daily. Faecal calcium was equal to dietary intake with low normal urine calcium. The slightly lowered faecal calcium in period 3 is exactly accounted for by slightly lowered faecal nitrogen, and is therefore due to variation in faecal collections. The net balance for calcium was negative. Phosphorus and nitrogen balance was positive.

Six-day Periods 4, 5, and 6.—Patient was given calciferol 10 mg. (400,000 units) daily by mouth. This resulted in a steady decrease in faecal calcium with a slight rise in urine calcium, bringing the patient into strongly positive balance for calcium and phosphorus. The rapidity of this response shows that the dose of calciferol was unnecessarily high. With the improvement in the calcium and phosphorus balance the serum inorganic phosphorus rose from 2.6 mg. to 3.6 mg. per 100 ml.

Discussion

Osteomalacia results from under-saturation of body fluids with respect to calcium and phosphate ions. This leads to a failure to precipitate calcium salts in the organic matrix of bone. It is manifested by a lowered serum calcium or inorganic phosphorus, or both, with demineralization of bones. The latter may be generalized or localized in the pseudo-fractures described by Looser, and which Albright and Reifenstein (1948) considered to be pathognomonic of osteomalacia.

Osteomalacia can occur from a variety of conditions which, by one means or another, lower the ionic product of calcium × phosphorus. These are now considered in relation to our own patient.

1. Dietary.—Deficiency of calcium salts or vitamin D. Our patient's diet contained a high proportion of bread and cheese containing adequate calcium salts, and was in fact deficient only in ascorbic acid, and even this had caused no signs or symptoms of scurvy.

2. Absorption Defect.—The commonest cause of osteomalacia in this country is steatorrhoea. The patient gave no history of bowel abnormality. A 12-day fat balance showed 93% of fat absorption on a daily intake of 80 g., during which time metabolic studies showed him to be in negative calcium balance. Moreover, a normal urine calcium excretion virtually excluded a diagnosis of steatorrhoea.

3. Renal Acidosis.—The patient did not have acidosis. Urine calcium was not high. He did not have aminoaciduria.

4. Resistant Rickets Group—Renal Tubular Defect with Hypophosphataemia.—Balance studies show that on a normal intake of calcium and phosphorus, and despite 0.25 mg. (10,000 units) of calciferol daily, he still failed to maintain a normal serum inorganic phosphorus and was in negative balance for calcium, mainly due to high faecal excretion. The positive balance for phosphorus was accounted for by the positive nitrogen balance. On administration of 10 mg. (400,000 units) of calciferol daily, the patient went into strongly positive calcium and phosphorus balance, and the serum inorganic phosphorus rose from 2.4 to 3.7 mg. per 100 ml. He has since been maintained on half of this dosage of calciferol, with remission of all symptoms and healing of his pseudo-fractures.

This type of balance chart is highly characteristic of cases of resistant rickets in adults or older adolescents. The total lack of response to 10,000 units of calciferol daily is quite unlike other types of osteomalacia, which are

particularly sensitive to these small doses (Bauer and Marble, 1932). On the other hand, the immediate and considerable improvement in calcium and phosphorus balance on massive doses of calciferol indicates that osteomalacia is present but "resistant" to doses of calciferol which would cure other types of the disease than resistant rickets. It has been shown by Bauer, Marble, and Claflin (1932) that normal subjects on large doses of calciferol will show a prompt improvement in absorption of calcium and phosphorus, but, unlike osteomalacics, there is an equally great increase in urinary calcium and phosphorus, so that the calcium and phosphorus balance is not improved. In our case the marked improvement in calcium and phosphorus balance on high doses of calciferol confirms that the patient was suffering from osteomalacia.

The histological criterion of active osteomalacia is the presence of excessive osteoid disposed as wide bands of palely staining tissue on the surface of both compact and trabecular bone. In the present case, although evidence of osteomalacia had been clear, the absence of this histological feature at the time of biopsy after three months of high dosage with vitamin D indicates that remineralization of osteoid had been effected.

Summary

Metabolic balance studies on a case of von Recklinghausen's neurofibromatosis with osteomalacia is presented.

The association of the two diseases is noted, and proved cases previously mentioned in the literature are quoted.

The aetiology of the osteomalacia is shown to be a renal tubular defect, presumably congenital, which brings it into the group of diseases usually known as resistant rickets.

Bone biopsy showed that there is osteoporosis as well as osteomalacia. The cystic appearance of bone is due to combined osteoporosis with deep indentation of bone by mucoid fibrous tissue originating from the periosteum. There was no histological evidence of osteomalacia at the time of biopsy, presumably as a result of treatment.

We wish to thank Dr. James Dow for referring this case to us; Mr. John W. Woollen for the serum analyses and fat balances; Miss Patricia Carroll for her help in the routine chemical investigations; and the nursing staff of the metabolic unit for their care of the patient during the prolonged periods involved in these balances.

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POST-OPERATIVE STAPHYLOCOCCAL ENTEROCOLITIS DURING ANTIBIOTIC THERAPY

BY

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Staphylococcal enteritis during antibiotic therapy is now of clinical importance. An antibiotic-induced intestinal bacterial vacuum in the recipient renders conditions very suitable for colonization by resistant staphylococci (Smith, 1952). Though chlortetracycline ("aureomycin") and oxytetracycline ("terramycin"), the most potent producers of an intestinal bacterial vacuum, have normally been incriminated, chloramphenicol, and penicillin and streptomycin together, have also been blamed. Zischka (1950), quoted by Herrell *et al.* (1953), even described a case following sulphaguanidine therapy. Parenteral administration has also produced the condition (Reiner *et al.*, 1952; Fairlie and Kendall, 1953; Herrell *et al.*, 1953). The normal post-operative increase in adrenocortical hormones may account for the infection gaining a hold, even in some cases without the aid of antibiotics (Herrell *et al.*, 1953). It seems justifiable to differentiate staphylococcal enteritis from post-operative pseudo-membranous enteritis; Prohaska *et al.* (1954), Dearing and Heilman (1953), and Pettet *et al.* (1954) are also of this opinion.

Cross-infection is the main factor in its causation. Cases have been described by Kramer (1948), Reiner *et al.* (1952), Dearing and Heilman (1953), Gardner (1953), Terplan *et al.* (1953), Wakefield and Sommers (1953), Hay and McKenzie (1954), Choremis *et al.* (1954), Williams (1954), Spink (1954), Bowie (1954), and Fairlie and Kendall (1953).

Three further cases are now recorded.

Case 1

A small, ill woman aged 68 had a strangulated femoral hernia repaired, 4 cm. of severely affected ileum being returned to the abdomen. She received 1 g. of streptomycin and 300,000 units of aqueous procaine penicillin intramuscularly twice daily for 4½ days. The streptomycin totalled 9 g. The wound suppurated and local infection increased over the next two days. The pus was not cultured. Her general condition deteriorated. Oral chloramphenicol, 0.5 g. six-hourly, was begun at 10 a.m. on the sixth day after operation. Two days later the wound was only slightly inflamed, and her general condition had so improved that provisional arrangements for her return home were made.

However, the next day she vomited several times and had severe diarrhoea. Her throat was red and sore. Chloramphenicol was stopped, a total of 6.5 g. having been given. She deteriorated with vomiting, diarrhoea, and circulatory collapse, and died ten days after operation.

At necropsy, otherwise healthy small and large intestines were full of a creamy and practically odourless light-yellow fluid. Acute infantile gastro-enteritis was simulated. This observation led to culture of the fluid, which gave a growth of coagulase-positive staphylococci insensitive to penicillin, sulphathiazole, streptomycin, chloramphenicol, and chlortetracycline. It was concluded that staphylococcal enteritis caused death.

Case 2

A man aged 35 with Crohn's disease received pre-operatively 26 g. of succinylsulphathiazole in 5½ days and streptomycin 2 g. and 1 g. on the two days before operation.

Right hemicolectomy was performed. Post-operatively he received 300,000 units of "distaquaine" and 0.5 g. of streptomycin intramuscularly twice daily. Apparently well, he passed a large loose stool on the evening of the day after the operation and a loose greenish stool the next morning. At 5.45 p.m. that day he collapsed with severe diarrhoea, dyspnoea, and cyanosis, lapsing into semicoma. The pulse was rapid and the blood pressure unrecordable. Penicillin and streptomycin therapy was discontinued. A total of 1.5 g. of intramuscular streptomycin had been given. Examination of a direct smear of anal discharge showed Gram-positive cocci, later proved to be *Staphylococcus aureus*.

Despite massive intravenous therapy his general condition failed to improve. Erythromycin, 400 mg., was administered via an indwelling Ryle's tube at midnight and again at 6 a.m. three days after operation with 0.5 g. of chlortetracycline intravenously. Diarrhoea continued. The patient died at 10.45 a.m. on the third post-operative day.

At necropsy a normal stomach contained 300 ml. of bile-stained fluid. Loops of intestine were bound together by thin fibrinous adhesions. The jejunum and ileum were acutely inflamed with a very red mucosa, containing much mucus and soft yellow exudate. The colon contained mucus and similar yellow fluid. The anastomosis was perfect. The exudate showed large numbers of Gram-positive cocci and relatively few faecal organisms, although a culture of anal discharge taken a few moments before death had shown enterococci only. Culture gave a growth of coagulase-positive *Staph. aureus*, enterococci, and coliform bacilli insensitive to penicillin and streptomycin.

Case 3

A stout, well-preserved woman aged 82 had a perforated gastric ulcer oversewn. Premedication had included 500,000 units of aqueous penicillin and 1 g. of streptomycin.

During a satisfactory post-operative course she received 300,000 units of distaquaine and 0.5 g. of streptomycin twice daily. Her bowels moved normally on the morning of the third day. However, at 2 p.m. the same day persistent vomiting and severe diarrhoea developed. Later, yellowish mucoid fluid was frequently voided. Her general condition rapidly deteriorated. Penicillin and streptomycin were stopped. The streptomycin given totalled 3.5 g. Despite intravenous fluid and chlortetracycline she lapsed into coma and circulatory failure, dying at 2 a.m. on the fourth post-operative day.

Necropsy showed an oversewn healing gastric ulcer in the fundus of the stomach. The small intestine was injected and contained thin pale fluid. No ulceration was present. Culture of the fluid gave a moderate growth of staphylococci, coagulase-positive and insensitive to penicillin and streptomycin. Enterococci and coliform bacilli were also present.

Discussion

Sudden severe diarrhoea, collapse, vomiting, and the finding in the intestinal fluid of staphylococci resistant to the antibiotic used were the salient features of these cases. The sudden onset and severe cholera-like course are noteworthy.

Under oral erythromycin the intestinal fluid in Case 2 became free from staphylococci. Nevertheless these organisms were obtained from the mucosa and membrane at necropsy. Terplan *et al.* (1953) recorded the same state of affairs. It probably represents the first stage in the elimination of the staphylococci.

Penicillin active against Gram-positive organisms and streptomycin against Gram-negative organisms are, when given together, similar in action to, but less powerful than, the wide-spectrum antibiotics. This paper and the experiences of Fairlie and Kendall (1953) and Choremis *et al.* (1954) show that penicillin and streptomycin given together can give rise to antibiotic-resistant fatal staphylococcal enteritis.

The advent of antibiotic-resistant staphylococci makes the administration of antibiotics potentially hazardous. Their prophylactic post-operative "umbrella" use in abdominal surgery becomes inadvisable. McKittrick and Wheelock (1954) could find in their cases no evidence that routine antibiotic measures, in the absence of specific indication, lessened post-operative morbidity. Moreover, should infection ensue after such routine use, there is a very real danger that the causative organism will be resistant to the antibiotics used.

Neither of the two patients treated responded to the intravenous fluid given. Frequent vomiting militates against efficacious oral therapy even though the staphylococci may be presumed to be still sensitive to erythromycin. Early diagnosis and, better, prevention is important.

Diagnosis is made on the clinical picture and confirmed by the finding of Gram-positive cocci in a direct smear of the anal discharge. Intravenous fluid replacement must be commensurate with the intestinal loss of fluid. Isolation nursing of the patient to limit spread of the numerous antibiotic-resistant staphylococci is required.

If in special cases wide-spectrum antibiotics have been used pre-operatively, a specimen of the bowel contents taken at operation should be cultured. Should staphylococci be found, treatment with erythromycin will avoid overt super-infection (Dearing and Heilman, 1953).

Though the poorly absorbed sulphonamides have greatly reduced sepsis in large-bowel surgery, the search for more thorough sterilization continues. Neomycin alone, or fortified with phthalylsulphathiazole or bacitracin, may be such an antiseptic (Fog, 1953, 1954; Poth, 1953; Anlyan *et al.*, 1954). These, however, produce the most complete and prolonged bacterial vacuum so far known. The possible advent of new clinical syndromes consequent upon the disturbance of the normal intestinal flora should be remembered (Smith, 1952). Animal experiments suggest that too thorough bowel disinfection renders implantation of carcinoma at a suture line more likely (Vink, 1954).

The lesson to be learned from these cases is that, at present, pre-operative large-bowel antisepsis should be obtained by the use of the poorly absorbed sulphonamides alone and that the combination of penicillin and streptomycin can give rise to staphylococcal enteritis. The use of penicillin and sulphadimidine has not, so far as I know, given rise to staphylococcal enteritis.

Summary

Three further cases, all fatal, of antibiotic-induced post-operative staphylococcal enteritis are reported.

Established cases respond poorly to treatment.

At present, pre-operative large-bowel antisepsis should probably be confined to the use of the poorly absorbed sulphonamides alone. With scrupulous anastomotic suturing, free from tension, an uneventful recovery should follow.

Post-operative use of wide-spectrum antibiotics should normally be reserved solely for the treatment of established complications of some magnitude.

Staphylococcal enteritis is a heavy price to pay for prophylaxis against possible sepsis.

It is now quite evident that in an attempt to banish the risk of sepsis in abdominal surgery—an infection which the unmolested patient will overcome provided it is not excessive or continuing—we may subject the patient to infinitely more serious hazards by the precipitate administration of wide-spectrum antibiotics.

I wish to thank Dr. D. Evans and Dr. I. MacKenzie for the bacteriological work; Mr. J. R. Ratcliffe and Mr. G. Harrison for access to the cases; and Mr. H. Blacow Yates and Mr. F. O'Gorman for help and encouragement in writing this paper.

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REPAIR OF INJURIES TO THE TENDONS OF THE HAND

BY

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In our country, Pirogov as early as the middle of the nineteenth century demonstrated experimentally the role of haemorrhage within the tendon sheath in the regeneration of damaged tendons. He was the first of many to contribute to the study of the circulation in relation to problems of regeneration and repair of tendon injuries.

During the last thirty-five years improvements in the surgery of tendon injuries have been made by Janelidse, Girgoloav, Rufanov, Gorinovskaya, Nikilaev, Rosov, Priorov, Kotschergein, Bogdanov, Grigorieva, Weinstein, Nikiforova, and others. They have studied the methods of foreign authors, and particularly of Bunnel, Iselin, Allen, and Mason. With this as a basis there has been issued a guide to surgeons on the treatment of these injuries related to factors such as the site, type of injury, and occupation of the injured worker. A number of points remain in dispute, but we believe that certain general principles have been agreed. I will attempt to outline our policy as concisely as possible.

If it were possible to exclude mistakes at the time of primary surgery in all medical institutions it would certainly greatly decrease the number of difficult problems of tendon repair, which so often lead to unsatisfactory results. The first condition for success in the treatment of tendon injuries is the availability of qualified surgeons able to carry out the necessary technical procedures immediately, carefully, and gently, in a well-equipped operating theatre, following early admission to hospital. The organization of the Health Service in the Soviet Union has endeavoured to make such treatment widely available.

We have put particular emphasis on the organization of the surgical care of industrial injuries. Every industrial plant includes a health department with a surgery for traumatic cases, and hospital beds are available day and night. This organization primarily means that surgery can be carried out within two hours of the accident. The operating surgeon retains responsibility for the patient until recovery is complete.

This report is based on the results of operations on tendon injuries of the wrist and fingers in 375 patients (see Table I). Special attention is paid to industrial injuries as shown in Table II. It will be seen that only 28 of a total of 123 patients had isolated injuries of the tendons, the remaining 95 had accompanying extensive skin defects, fractures, or nerve lesions. These complications must be taken into account in evaluation of our surgical technique.

TABLE I.—*Summary of Data of Soviet Surgeons on Primary Tendon Suture*

Author	Year	No. of Cases	Site		Good Results (%)	
			Flexors	Extensors	Flexors	Extensors
Weinstein ..	1936	71	26	45	42	80
Svigaskaja ..	1938	131	76	55	81	82
Atanov ..	1939	83	34	49	82	67
Michelson ..	1939	92	92	—	40	—
Choranov ..	1941	40	24	16	83	100
Grigorieva ..	1948	106	49	57	65	95
Lebedev ..	1951	70	45	25	64	100
Rosov ..	1951	444	189	255	71	86
Bogdanov ..	1953	355	167	188	75	89

TABLE II.—*Types of Industrial Injuries to Tendons of the Hand*

With fracture	43
Isolated injuries	28
With fracture and defects of soft tissue	19
With soft tissue defects	19
With damage to nerves and blood vessels	7
With injury to joints	7
	123

Primary Suture

As a first-aid measure we insist on the immediate immobilization of the hand, with the fingers flexed into a fist for damage to the flexor tendons, and with the fingers extended in rupture of the extensors. This prevents retraction of muscles and torn tendon ends and facilitates primary surgery.

The role of surgery is then to transform the accidental wound into a surgical wound. Operating early with adequate assistance, we aim at accurate suturing of damaged nerves and tendons. This is followed by accurate skin apposition or grafting. Fractures are immobilized in the required position. Primary and accurate surgery during the first hours after injury can make a great contribution to the results obtained in these injuries. Primary suture of tendons restores the anatomical relations of the tissues; it removes a situation in which abnormal nerve impulses are engendered by the damage; it contributes to the re-establishment of normal physiological interrelations between the central nervous system and the local motor apparatus; and it predisposes to early recovery of function without rigidity or contracture.

Primary suture, if antibiotics are available, is in our opinion indicated for all tendon injuries when an experienced surgeon is available, except in the "no-man's-land" area. Outside this zone there are absolutely no contra-indications to primary suture even with fractures or skin defects, unless associated with severe disturbance of the circulation. The results of treatment depend not so much on the extent of the damage as its site.

We do not agree with those authors who state, "Repair in 'no-man's-land,' from the middle palmar crease to the middle finger crease, as a rule must be secondary." Primary suture within this zone is permissible, particularly in clean-cut incised wounds, if the hand has been at once correctly immobilized. We have rejected tendon sutures on the palmar surface with silk, and use capron. We permit the use of silk in the reconstruction of extensor tendons. Primary suture is not indicated: (1) If the surgeon is in any doubt about the efficiency of its use in the "no-man's-land" area. (2) In flexor tendon injuries in this region if the accident has occurred with the fingers flexed. In these cases, search for the retracted tendon ends necessitates a larger incision, with damage to the gliding mechanism. Suture is not desirable within the fibro-annular pulleys of the palm and phalanges. (3) In extensive injuries of palmar soft tissues or fractures of the distal part of the metacarpals or proximal phalanges with displacement.

Primary suture in isolated rupture of the profundus tendon over the middle phalanx distal to the bifurcation of sublimis may be carried out by direct suture.

In injuries of the long flexor to the thumb, the proximal end can usually be found between the two heads of origin of the short flexor. Where suture cannot be carried out here, free grafting will be necessary.

It is well known that the results of primary tendon suture vary with the mechanism of the injury. When the palm of the hand has been damaged by falling on a sharp cutting object with the fingers extended, the proximal end of the tendon, although displaced to the base of the palm, can be found and confidently sutured. In injuries to the palm with the fingers closed into a fist, as, for example, in grasping the blade of a knife, the distal end of the tendon retracts, primary suture is difficult, and its results are less satisfactory.

Most of these operations are carried out by us under local analgesia without a tourniquet, or under intraosseous analgesia with a broad pneumatic cuff. Careful use of this method can prevent the formation of a haematoma. Esmarch bandages are not used. Occasionally we operate under inhalational anaesthesia.

The technique of suture must be speedy, simple, and stable. To be stable the tendon must be crossed without damaging its circulation. The suture must be countersunk in the tendon so that only a minimal amount is left on the surface to interfere with gliding. We use a modification of the method described by Cuneo.

Primary tendon suture has given excellent and satisfactory results in 75% of flexor and 89% of extensor tendon injuries.

Delayed Suture

The second group comprises those in whom primary suture has not been carried out. These cases have been operated on 21 to 45 days after injury, when the inflammatory reaction has settled; occasionally later. In the majority we have succeeded in uniting the severed tendons by delayed suture, and only occasionally have we required to use grafts for injuries in the "no-man's-land" area or beneath the carpal ligament. If problems of skin cover do not interfere, the earlier we operate the easier is the operation found to be and the better its results. In our experience, with early surgery, the dense adhesions between the retracted ends of the tendons and the intermediate structures had not yet formed. Good mobility of the joints is one of the conditions which determine the success of surgery. Only on two occasions (on the 29th and 57th days) have we found extensive fibrous thickening with involvement of the tendon in deep scarring. We have excised these scars as is our practice in Dupuytren's contracture. We have then isolated and sutured the deep flexor proximal in the "no-man's-land" area, using a capron suture.

Where there has been delayed healing of a laceration of the palm or the fingers with extensive scarring we do not rush into reconstructive surgery. We use physiotherapy, including baths, to restore movement and circulation to the skin. Three days before operation we clean the operating field and keep the hand in a sterile bag. We have found it very necessary to remove damaged scarred skin in the palm, and to replace it by some form of plastic procedure, in order to obtain satisfactory results in tendon repair. It is well recognized that secondary repairs to flexor tendons in the zone of "no-man's-land" are very difficult, particularly where the pulleys are destroyed.

Our incisions run parallel to the palmar crease and are curved to the base of the hypothenar eminence. When both ends of the injured tendon or tendons have been located, the distal tendon with its scars may be removed from the sheath and from beneath the pulleys without damage to the annular ligament. We use special instruments designed by Rosov. The freed channel is filled by a free graft derived preferably from the long extensor of the third or fourth toe.

The paratenon is preserved, and is prevented from displacement by a stitch. The graft must exceed the length of the "no-man's-land" area. After extraction of the

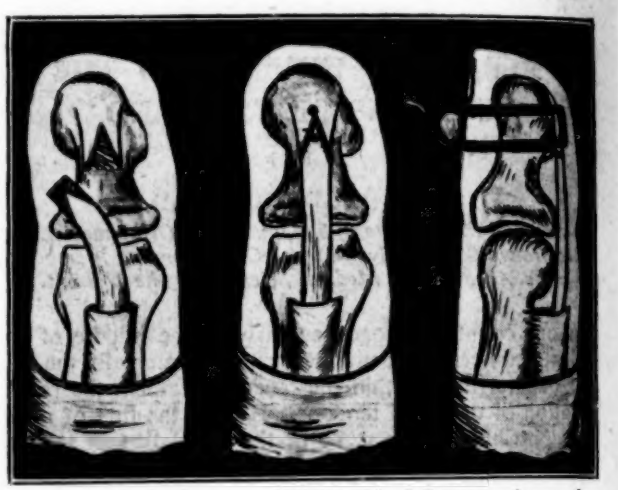

FIG. 1.—Method of suture of distal end of flexor tendon graft.

graft it is sutured at the distal end to the bone of the distal phalanx. A wedge is cut in the distal tendon reaching to the bone. With the finest possible awl two holes are made which perforate the bone to the dorsum. The graft is then sutured to the bone by a stitch which is tied over a dorsal bolster of gauze. The sides of the wedge of the distal tendon are then sutured to the graft as described by Allen (Fig. 1). The stitch is withdrawn after three weeks.

The proximal graft is sutured side by side to the proximal end of the deep flexor tendon. Where both tendons have been injured we are convinced that only profundus should be sutured. In patients with multiple injuries to flexor tendons we operate by stages; firstly by repairing the tendons of two fingers only, and delaying reconstruction of the remaining tendons to a second stage. In cases of destroyed annular ligaments, Rosov, Dubrov, and Nikolaeva reconstruct them with free fascial flaps or by transplants from the extensor tendons of a toe. We have no personal experience of this method, and use a flap from the underlying lumbrical muscle.

In 25% of primary operations we have had good results with nearly full flexion and adequate extension. In 50%, flexion was adequate but not full. When the patient was not satisfied with the end-result because the tip of the finger did not reach the palm, we proposed a second operation—arthrodesis of the distal joint in 25 degrees of flexion. By

this means we improved the end-results in seven patients. The others refused the secondary operation and adjusted themselves to their work.

In the repair of tendons beneath the carpal ligament we usually use free grafts. If the median nerve is divided we suture it at the same time. In late cases with multiple damage to the tendons in this area we have sometimes been obliged to excise the carpal ligament in order to envelop the tendon suture with loose cellular tissue.

FIG. 2.—Pathology and treatment of injury to the extensor of the proximal interphalangeal joint.

Considerable attention has been paid by us to injuries of the extensors of the proximal interphalangeal joints. The patient loses the capacity to extend the middle phalanx, and the shortened muscles provoke hyperextension of the distal phalanx. We have attempted to repair this by a method worked out by Weinstein (Fig. 2).

A long curved incision reaching to the middle of the base of the phalanx exposes the extensor aponeurosis over the proximal joint. The proximal aponeurosis is dissected out so as to define the lateral bundles. These are approximated with the finger in extension, with five or six fine sutures. The proximal stitches include not only the lateral bundles but also the middle bundle of the long extensor (Fig. 2).

Post-operative Treatment

After tendon repairs it is necessary to immobilize the hand in plaster for four weeks, to prevent retraction of the sutured tendon ends. Following repair of the flexor tendons, the plaster is applied to the back of the hand and forearm to stabilize the fingers in a position of flexion. In injuries of the extensor tendons the splint is applied to the palmar surface with the fingers extended.

The hand is elevated for three to four days after operation. Stitches are removed on the 9th or 10th day, and the patient is discharged from hospital. From the 21st day movement of the fingers is allowed. After six to eight weeks the patient returns to light work, progressing gently to full work after three months.

Aftercare includes physiotherapy and baths, started from the 15th day. The patient also receives corticotrophin, which we have found to help in preventing scar formation and in the absorption of scarring around the repaired tendons. The surgeon who has carried out the operation must keep his patient under personal observation, and should certainly see him at least twice a week. At the end of the third week the surgeon must direct active exercises, with gentle use, to ensure the best possible function.

Conclusion

In extensor tendon injuries, plastic repairs have given satisfactory results in 85% of the patients. Tendon repair on the palmar surface has given satisfactory results in 77%, including 65% in the area of "no-man's-land."

INCISION FOR GALL-BLADDER SURGERY

BY

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The two incisions generally used for operating on the gall-bladder are the right upper paramedian and Kocher's incision. The paramedian incision is often chosen when the costal angle is narrow, and Kocher's when the costal angle is broad.

Kocher (1895) described his incision as an obliquely transverse incision 10 to 15 cm. long, made at a distance of 4 to 6 cm. from the costal margin. As generally carried out in this country it is 2 to 3 cm. from and parallel to the costal margin, care being taken at its lateral extremity to spare the ninth costal nerve. I was deterred from using Kocher's incision by seeing post-operative scar herniae after its employment, but for the past seven years have utilized with increasing frequency a modification which has the advantage of dividing the rectus sheath in the direction of the fibres of its main component—namely, the aponeurosis of the internal oblique. As a result, any straining after operation by tensing the external and internal oblique and transversalis abdominal muscles tends to approximate the fibres of the rectus sheath. It is essentially a muscle-splitting operation so far as the rectus sheath is concerned and so is easy to close, and the stitches do not subsequently cut out. Compared with any vertical incision the patient is far more comfortable after operation, breathing, bending, and moving easier. Normally, patients get out of bed the day after operation. I have never seen a scar hernia follow its use.

Technique

The incision (Fig. 1) is from the midline, one handbreadth —3½ in. (9 cm.)—above the umbilicus to the tip of the tenth right costal cartilage. In some fat patients there is a natural skin crease in this line which can be utilized. The skin,

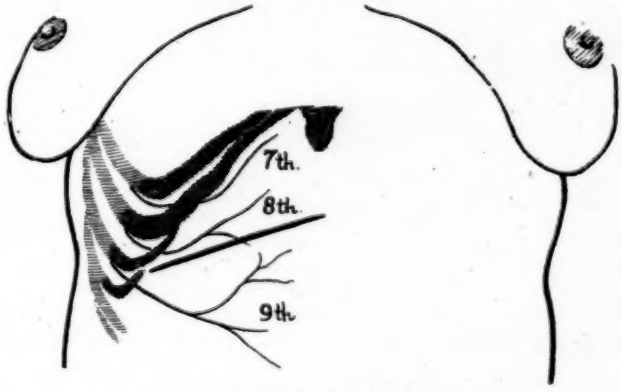

FIG. 1.—The line of incision.

the subcutaneous tissue, the anterior rectus sheath, and the rectus muscle are divided in the line of the incision as far out as the outer border of the rectus abdominis (Fig. 2). The medial two-thirds of the posterior rectus sheath with the underlying peritoneum is cut in the same line, then the transversus abdominis is split laterally in the direction of its fibres.

When cutting the fibres of the rectus muscle, branches of the superior epigastric require ligation one-third and two-

thirds of the way across the muscle. More length is seldom required laterally unless it is desired for mobilizing the duodenum. It can be obtained by splitting the external and internal oblique and the transversalis muscles in the direction of their fibres. This incision over the gall-bladder gives an excellent exposure of the biliary passages and it is

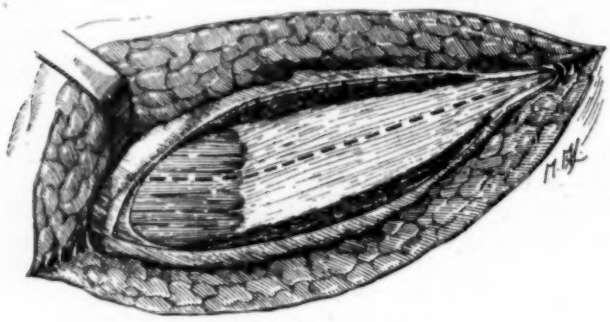

FIG. 2.—The incision completed.

easy to explore the common bile duct and, in the average case, to pass the standard Desjardins forceps down this duct. For a barrel-chested patient with a high liver I have a more curved pair of Desjardins forceps available. Should more room be required medially the incision is extended through the linea alba into the left rectus sheath. As the incision lies between the eighth and ninth intercostal nerves, these nerves are in no danger of injury and do not have to be identified (Fig. 1). Should the lateral margin of the incision be made a little low the ninth intercostal nerve is seen lying on the posterior layer of the rectus sheath near its lateral margin. The direction of the ninth nerve at this point is that taken by the ninth rib in the axilla (Fig. 1).

Anatomical Points

Identification of Ninth and Tenth Costal Cartilages

The tenth costal cartilage can be felt by running the finger outwards along the smoothly curving lower costal margin till a definite step is felt, which is caused by the tenth costal cartilage. Fig. 1 shows the usual way the tenth cartilage turns up to form this step. In two cases the tenth rib was floating and did not articulate with the ninth, reminiscent of the three floating ribs of the anthropoids. The narrow spear-like tip of the ninth costal cartilage can be felt only by taking the ninth costal cartilage between the right finger and thumb, where it is lying along the postero-inferior border of the costal margin, and, by moving it, to feel with the other hand its sharp tip where it articulates with the broad eighth costal cartilage. This identification of the tip of the ninth is not a necessary step of the operation, but it is of interest in the diagnosis of gall-bladder tenderness, which is situated most commonly 1 in. (2.5 cm.) below the tip of the ninth costal cartilage on a line drawn from the tip of that cartilage to the umbilicus. It is the surface marking of the infundibulum (Hartmann's pouch), where, with the patient supine, stones tend to gravitate.

Direction of Fibres in Rectus Sheath

On exposing the anterior layer of the rectus sheath, fibres of the external oblique are seen running downwards and medially across the line of the incision. If, however, the anterior rectus sheath is inspected on its deep side the fibres of the internal oblique are running upwards and medially along the line of the incision. The external oblique aponeurosis becomes fused with the internal oblique about a quarter of the way from the lateral border of the rectus sheath (Fig. 3).

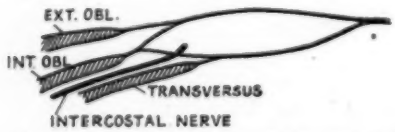

FIG. 3.—Showing fusion of the external oblique aponeurosis with the internal oblique.

The posterior layer of the rectus sheath shows the stout fibres of the internal oblique running upwards and inwards along the line of the incision. The red muscular fibres of the transversus abdominis show through the outer third of the posterior layer of the sheath. These muscular fibres run transversely as a thin aponeurotic layer which becomes fused with the posterior rectus sheath at the junction of the outer and middle thirds of the sheath. The transversus aponeurotic fibres are by far the weaker component of the posterior rectus sheath.

Course of the Intercostal Nerves

The ninth intercostal nerve leaves the subcostal groove about the mid-axillary line and runs downwards and forwards, passing behind the tenth costal cartilage where the cartilage is turning up (Fig. 1). It lies on the transversus muscle and is below the line of the incision. The eighth intercostal nerve as it passes behind the ninth costal cartilage is directed upwards and medially and is above the line of the incision. In dividing the rectus muscle a fine twig connecting the eighth and ninth nerves can occasionally be seen. The line of incision runs between these nerves (Fig. 1).

Anatomical dissections by Davies, Gladstone, and Stibbe (1932) have shown that the rectus muscle does not receive a segmental supply from one intercostal nerve. As a result of communications in the thorax, and again between intercostal nerves when lying on the transversus abdominis muscle, any one segment of the rectus is supplied by at least three intercostal nerves. The division of any minor connecting branch in the rectus muscle does not affect the strength of the rectus muscle when the incision is healed.

I wish to thank Sir Wilfrid Le Gros Clark for drawing my attention to the work of Davies, Gladstone, and Stibbe and to the skeleton of the anthropoid, and to Miss M. C. McLarty for the drawings.

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MULTIPLE TOXIC EFFECTS OF PHENYLBUTAZONE

REPORT OF A FATAL CASE

BY

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It is almost four years since Currie (1951) first drew attention to the therapeutic effect of phenylbutazone ("butazolidin"). Since then it has been employed extensively both in hospital and in general practice, and many reports on its use, mainly in the treatment of rheumatoid arthritis, have appeared in the medical press. There is general agreement that the drug has a marked analgesic action in rheumatoid arthritis in roughly one case in three, but it is doubtful whether it has any anti-inflammatory properties. As Hart (1953) pointed out, although occasionally a reduction of inflammatory swelling is seen, increase in range of movement and function tests, and decrease in stiffness, are essentially secondary to the relief of pain. Steinbrocker (1953) reported on the results he had obtained in a large series of patients on short- and long-term phenylbutazone treatment, and came to the conclusion that the drug was a powerful analgesic but that its antirheumatic effect, if any, was slight.

Since the introduction of phenylbutazone in the treatment of the rheumatic diseases numerous reports of its

toxic effects have been published, the incidence varying between 20 and 50%. While the majority of the side-effects are of a mild nature, serious complications have been encountered from time to time, and a not insignificant number of fatalities have been attributed to the use of this drug. Deaths due to agranulocytosis (*British Medical Journal*, 1952; *Lancet*, 1953; Newns, 1953; Etess and Jacobson, 1953; Steinberg *et al.*, 1953; Dilling, 1953; Wood, 1954), aplastic anaemia (Leonard, 1953), haematemesis (*British Medical Journal*, 1952), perforation of a peptic ulcer (Benstead, 1953), and to renal failure (Bruck *et al.*, 1954; Johnson and Larkin, 1954) have been recorded. The non-fatal complications are by now well known, and include sodium retention with oedema, various types of skin rashes, activation or perforation of a peptic ulcer, agranulocytosis, thrombocytopenia, nausea, vomiting and diarrhoea, jaundice, and bleeding manifestations with resultant anaemia—for example, haematemesis, melaena, and haematuria. Many patients have experienced two or more complications at the same time (Hart, 1953; Pemberton, 1954). The following case, which had a fatal termination, is of interest in that multiple toxic reactions, including a polyneuritis, made their appearance during the administration of phenylbutazone.

Case History

A single woman aged 41 was admitted to hospital on July 3, 1953, with a history of rheumatoid arthritis of seven years' duration, involving her hands, wrists, ankles, and feet. Six months before admission her doctor put her on phenylbutazone, when she was given 600 mg. a day for one week, 500 mg. a day for two days, and then 400 mg. for one day. The drug had to be discontinued at this point on account of a haematemesis of moderate severity. This was accompanied by ulceration of the mouth and lips. Recovery from the haemorrhage was rapid and the buccal ulcers healed. Six weeks later her joints became so painful that she persuaded her doctor, against his better judgment, to let her resume the phenylbutazone. She was put on 200 mg. daily, and this gave her considerable relief from pain. She was maintained on this dose for three months, when a rash appeared on her legs and the drug was stopped. After a few days the ulcers reappeared in her mouth and mild jaundice was noted by her doctor. Two weeks later she developed weakness of her arms and legs, and within a week she was unable to move her arms or legs. This was unaccompanied by pain.

On admission she was seen to be a thin and ill-looking woman with a sallow complexion, and lay limply in bed. She was afebrile, with a mild tachycardia. There was no evidence of jaundice. Multiple small punched-out ulcers were present on the ankles and feet, and a few superficial ulcers were seen on the lips and in the mouth. There was loss of all types of sensation in the arms below the elbows and in the legs below the knees. Weakness of the shoulder-girdle and hip muscles and complete loss of power below the elbows and knees were present. All deep reflexes in the arms and legs were absent; the plantar responses were flexor. There were chronic rheumatoid changes in the fingers, wrists, knees, ankles, and feet. The liver and spleen were not palpable. The heart and lungs were normal.

Laboratory investigations on admission resulted as follows: haemoglobin, 65%; red blood cells, 3,750,000; white blood cells, 11,800; blood film, normal; erythrocyte sedimentation rate (Westergren), 96 mm. in one hour; blood W.R., negative; blood urea, 30 mg. per 100 ml.; blood uric acid, 1.9 mg. per 100 ml.; plasma proteins, normal; thymol turbidity, 3 units; thymol flocculation, positive after 4 hours; alkaline phosphatase, 3.5 K.A. units per 100 ml.; van den Bergh, negative; icterus index, 4; urine: no sugar, albumin, bile, or urobilin; faecal occult blood, positive.

In spite of intensive medical measures, physiotherapy, and splintage, her condition slowly deteriorated and she became emaciated. Flexion contracture of the fingers and subluxation of the knees developed. She was unconscious for three days before she died on January 28, 1954, seven months from the date of admission.

Necropsy.—The body was that of an extremely emaciated woman with numerous pressure sores over the bony prominences. A moderate degree of rheumatoid arthritis of the fingers, wrists, knees, and ankles was noted. The heart appeared normal. The lungs showed evidence of a bilateral bronchopneumonia with abscess formation. Abdomen: a lesser-curvature posterior-wall chronic ulcer, 12 by 7 mm., with a small perforation and associated peritonitis, was found; the liver weighed 1,140 g. and was soft and pale; a few small gall-stones were present in the gall-bladder, which was small and had a thickened wall; the spleen was congested; the genito-urinary organs were normal. Endocrine glands: the pituitary, thyroid, and adrenals were normal. Apart from some general pallor and oedema, the brain was normal. Macroscopically, no gross abnormality was seen in the spinal cord or peripheral nerves.

Histological Examination.—There was evidence of a widespread polyneuritis with marked degeneration and vacuolation of the posterior columns of the cord. Both median nerves showed almost complete loss of myelin sheaths and very severe loss of axis cylinders. The ulnar nerves presented a similar but slightly less marked appearance. Many nerve bundles in the sciatic nerves looked shrunken, and the myelin sheaths stained irregularly, but the axis cylinders were well preserved. The liver showed a moderate degree of fatty infiltration around the portal tracts. There was no evidence of central necrosis. The spleen was normal. Some focal cellular infiltrate and tubular atrophy, with an occasional damaged glomerulus, were seen in the kidneys. A bronchopneumonia with abscess formation was present in both lungs.

Discussion

This case presents some interesting features. The patient received a total of only 5.6 g. of phenylbutazone prior to the haematemesis, which was of moderate severity. Careful questioning did not reveal any previous history of gastric disturbance. In addition to the haemorrhage, superficial ulceration of the mouth and lips was noted, a finding which may well have reflected the state of the gastric mucosa at that time. Multiple superficial gastric erosions were reported at necropsy by Dilling (1953) in a case of fatal agranulocytosis following phenylbutazone therapy.

It is obvious that treatment with phenylbutazone should have been permanently discontinued at this point, but six weeks later it was resumed at the patient's own request, and she was maintained on it for a further three months, when the second series of side-effects made their appearance.

It will be seen that this patient had six complications in all. Four of these—namely, ulceration of the mouth, rash, haematemesis, and perforation—could be directly attributed to the administration of phenylbutazone, as all are now accepted as toxic effects of the drug and have been reported on frequent occasions. Whether the jaundice and polyneuritis were associated with the use of the drug is difficult to establish, for as Currie *et al.* (1953) pointed out, not all symptoms occurring during drug therapy are necessarily due to the drug. While jaundice, mainly of the obstructive variety, has been reported from time to time (Bourne, 1953; Solomon, 1953), post-mortem examination in this case revealed several small calculi in the gall-bladder and only some fatty infiltration of the liver. The icterus, therefore, could have been due either to obstruction of the common bile duct by a gall-stone or to a mild toxic hepatitis, followed by regeneration of liver tissue.

Headache and vertigo have occasionally been encountered during phenylbutazone therapy, but neurological signs are apparently rare. Loxton *et al.* (1952) reported a case which developed a lesion of the central nervous system with

paralysis of the left leg and urinary incontinence and which they attributed to a haemorrhagic transverse myelitis. While the evidence incriminating phenylbutazone as the cause of the polyneuritis in the present case is purely circumstantial, no other aetiological factor could be demonstrated.

The immediate cause of death was presumably the acute peritonitis resulting from perforation of the gastric ulcer in an emaciated and moribund subject. Clearly, a fatal issue could, and should, have been avoided if the phenylbutazone therapy had been permanently discontinued by her doctor at the time of the haematemesis. It demonstrates once more how vital it is that medical men should not be influenced in their judgment by the entreaties of the patient.

It is generally accepted that phenylbutazone is rapidly absorbed when given by mouth. Pemberton (1954) regarded a blood concentration of 12–16 mg. per 100 ml. as the therapeutic range of the drug. On the other hand, Currie *et al.* (1953) found that an initial blood concentration of 8–11 mg. per 100 ml. was sufficient to suppress the symptoms, and that remission could be maintained by much lower concentrations—4.6 to 8 mg. per 100 ml. Bruck *et al.* (1954) obtained maximal suppression of symptoms in their series at any level between 5 and 10 mg. per 100 ml. Phenylbutazone is slowly eliminated from the body (Burns *et al.*, 1952), and appreciable levels remain in the blood for at least two weeks after the cessation of treatment (Pemberton, 1954). Toxic effects, therefore, can be expected after the drug has been withdrawn. Shields *et al.* (1953) reported a case in which perforation of a gastric ulcer occurred seventy-two hours after discontinuation of phenylbutazone therapy, and Wood (1954) a case in which a rash appeared six days after the drug was stopped.

Some observers (Bruck *et al.*, 1954) have found a striking correlation between the frequency of toxic reactions and the blood phenylbutazone level, while others (Leonard, 1953; Nassim and Pilkington, 1953; Pemberton, 1954) have failed to confirm this observation, and feel that the administration of small doses of phenylbutazone does not eliminate the possibility of the occurrence of toxic side-effects. In the case reported here a moderately severe haematemesis with ulceration of the mouth and lips developed after a total dosage of only 5.6 g., the maximum dose being 600 mg. a day. This raises the question whether the toxic effects of phenylbutazone are due entirely to overdosage or whether an idiosyncrasy to the drug may be responsible in certain cases. Support for the latter view has been produced by O'Brien and Storey (1954), who recorded a case in which they attributed the cause of death during phenylbutazone therapy to a hypersensitivity reaction, which was manifest histologically by three types of lesion: polyarteritis nodosa, hypersensitivity angiitis, and granulomatous lesions. A severe case of sensitivity to phenylbutazone with the features of Stevens–Johnson syndrome and granulocytopenia was described by Steel and Moffatt (1954). It has also been suggested that agranulocytosis may be due to an idiosyncrasy to the drug (Stifel and Burnheimer, 1953), and that the drop in the white-cell count is sudden, so that daily counts, which give a false sense of security, are of doubtful value in anticipating this complication.

If toxic symptoms develop during phenylbutazone therapy the drug is generally withdrawn either temporarily or permanently, according to the nature and severity of the reaction. Many observers advocate the resumption of the drug, usually on a smaller dosage, once all signs of the reaction have disappeared, except in cases with the more serious complications. In this connexion, Fishman and Reynolds (1953) issued a warning, stating that it was unwise to resume treatment with phenylbutazone, however mild the toxic effects. They reported the case of a woman who received phenylbutazone for a whiplash injury of the neck following a car accident. A mild rash appeared after she had taken sixteen 200-mg. tablets, and was of the morbilliform type. This began to subside fairly quickly with treatment and omission of the drug, and had almost disappeared when, for no obvious reason, it suddenly flared up again and developed into an exfoliative dermatitis which nearly proved fatal.

My experience with the present case, added to an overall incidence of 26% of toxic reactions, including four patients with severe haematemeses, forces me to the conclusion that phenylbutazone is a dangerous drug and that the risks attached to its use in rheumatoid arthritis are not outweighed by its advantages. As it is still widely employed in general practice, where for obvious reasons patients cannot be kept under the strictest supervision, I feel that the publication of reports on its toxic effects may act as a deterrent to its use in the treatment of rheumatoid arthritis. In its place one would recommend aspirin, given in maximum tolerated doses as described in the recent Medical Research Council and Nuffield Foundation Report (1954).

Phenylbutazone, however, would appear to be an effective therapeutic agent in the acute stages of gout (Huffman *et al.*, 1954) on which it has a marked uricosuric effect. The majority of acute attacks of gout are brought under control within 8–12 hours, and the drug need be given only for a matter of days, thus greatly reducing the danger of side-effects.

Summary

The literature on the toxic effects of phenylbutazone therapy in rheumatoid arthritis is briefly reviewed.

A fatal case is reported in which six complications developed during the administration of the drug—namely, ulceration of the lips and mouth, a rash, haematemesis, perforation of a gastric ulcer, jaundice, and a polyneuritis—and their causal relationship to the use of the drug is discussed.

The possible factors in the production of side-effects are mentioned.

It is felt that phenylbutazone is a dangerous drug and should not be employed in the treatment of rheumatoid arthritis, and that aspirin given in maximum tolerated doses is as effective and much less toxic.

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A CASE OF STEVENS-JOHNSON SYNDROME WITH EXTENSIVE SURGICAL EMPHYSEMA

BY

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The condition known as Stevens–Johnson syndrome, a skin eruption resembling erythema multiforme, with lesions of the mouth, conjunctivae, genitalia, and anus, was described by Stevens and Johnson in 1922. A similar condition had been recorded in the last century, but does not appear to have been thought worthy of special notice. The cause of the disease is unknown. It is suggested that the eruption may be due to hypersensitivity or allergy, because some cases give a history of recent upper respiratory infection or of the administration of sulphonamides. A virus has been suggested, but at present there is no proof of this. The condition usually runs a benign course, with full recovery in ten days, but respiratory complications may occur (Liddle, 1951).

The following case of Stevens–Johnson syndrome is reported because of its severity and because of the unusual complication of surgical emphysema.

Case History

A boy aged 9 years 11 months was admitted to hospital on May 1, 1954, with the following history. Five days previously he had complained of headache, and was listless. His throat and conjunctivae were inflamed, and his temperature was 102° F. (38.9° C.). He was started on a course of "tresamide" (each 0.5-g. tablet containing sulphamerazine 0.1 g., sulphadiazine 0.2 g., sulphacetamide, 0.2 g.), which was replaced by chloramphenicol on the fourth day of the illness because of the appearance of a morbilliform rash on the chest. On the next day the rash spread all over the face, chest, and limbs, and many of the lesions became vesicular. He had severe toxaemia, headache, and nausea, and his temperature rose to 105° F. (40.6° C.).

He was admitted to an isolation hospital as a suspected case of smallpox, and thereafter transferred to the Grove Hospital on the sixth day of the illness.

On admission he was seen to be a well-built boy, with no history of previous illness. He was semicomatose and profoundly toxaemic. His temperature was 99° F. (37.2° C.), pulse 108, and respirations 20. There was the dusky-red rash of erythema multiforme on the face, neck, trunk, and limbs. In places the rash was confluent and there were many large vesicles containing yellow fluid. Some vesicles had burst, particularly round the eyes, ears, and neck, and the underlying dermis was fiery red. The lips were purplish, cracked, and bleeding. The buccal mucosa was overlaid with collapsed vesicles, and gingivitis and ulceration of the tongue were present. The conjunctivae were deeply injected and oedematous. He had photophobia, but no corneal lesions were seen. There was some ulceration of the glans penis and dysuria, probably due to lesions within the meatus. There was no urethral discharge. Gross surgical emphysema was present on the chest, stretching from the neck to the lower abdomen. Respiration was a little laboured and there was a suggestion of cyanosis. Anteriorly, breath and heart sounds were difficult to hear, but auscultation of the back of the chest revealed moist crepitations in all areas. The spleen and liver could not be felt. A diagnosis of Stevens–Johnson syndrome was made.

The patient was placed in an oxygen tent and parenteral penicillin (250,000 units six-hourly) and streptomycin (0.5 g. six-hourly) were given. On the day after admission the general condition was unchanged and the surgical emphysema had spread downwards to the groins and into the upper parts of the thighs. In the region of the lower ribs large pockets of air were palpable under the skin.

On the fifth day after admission exudation into the vesicles was maximal, with dehydration and circulatory collapse. The temperature rose to 104° F. (40° C.), and the pulse was frequent and weak. Intravenous plasma was given (3 pints—1.7 litres) as it was thought that protein loss in the exudate was high. The plasma was followed by glucose–saline. Intravenous therapy was continued for two days, after which the patient's condition began to improve. On the sixth day, when the mouth lesions were clearing, oral chlortetracycline was given (250 mg.) six-hourly, in place of the penicillin and streptomycin. By the tenth day the rash had begun to fade and the raw areas were drying. There was heavy desquamation of the hands and feet. By this time the conjunctivae were nearly normal, and there were no corneal lesions.

The chest was slow in clearing. Three weeks after admission the patient was still raising much thick sputum, although by then the pyrexia had subsided. From the third week onwards recovery was uninterrupted. The patient was discharged after five weeks, the only sequelae being some staining from the rash and loosening of all finger- and toe-nails.

Chest X-ray Examination.—Films were taken on the third, seventh, and twelfth days after admission. In the first film pronounced surgical emphysema was seen in the soft tissues of the neck and thoracic wall, but the lungs were clear. On each side of the superior mediastinum thin vertical lines of opacity were visible. These lines appeared to represent lateral displacement of the mediastinal pleura, suggesting the presence of mediastinal emphysema. The second film showed patchy shadowing of the lung fields, and the mediastinal appearances were the same. The final film showed some left basal collapse, the surgical emphysema was less marked, and the mediastinal pleura was no longer displaced.

Comment

This case represents a severe form of the Stevens–Johnson syndrome, in which skin, mucous membranes, and respiratory systems were all heavily affected. In addition there was severe toxaemia. The chief point of interest was the surgical emphysema which occurred early in the disease and which persisted for nearly three weeks. The likely explanation for the surgical emphysema seems to be as follows. In respiratory infections, such as pertussis, influenza, or measles, and in bronchial asthma, valvular obstruction of terminal bronchioles may be produced by mucous plugs or by inflammatory oedema of the lining mucosa. Alveolar air trapped behind the obstruction may be forced into the interstitial spaces of the lung by expiratory pressure. The air may then pass along the vascular sheaths (Aisner and Franco, 1949), to reach the hilum and thence the mediastinum. Air may then escape from the mediastinum into the tissues of the neck.

Similar cases of mediastinal emphysema have been described in association with the muscular straining of parturition (MacRae, 1949) and the lifting of heavy weights. Here the expiratory muscles are forcibly contracted with the glottis closed, causing rupture of alveoli.

In the present case it seems probable that the obstruction was caused by thick mucus or by the swelling of the mucosal lining of the small air passages.

The area of collapse seen in the third *x*-ray film may be significant. Possibly it marks the site at which a number of bronchioles became obstructed, causing the air in the alveoli distal to the obstruction to be forced into the vascular sheaths of the lung.

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PARAPLEGIA FOLLOWING THE USE OF "EFOCAINE"

BY

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"Efocaine" is a long-acting local analgesic consisting of a solution of 1% procaine base, 0.25% procaine hydrochloride, and 5% butyl-*p*-aminobenzoate in a solvent composed of 2% polyethylene glycol-300, 78% propylene glycol, and water. It also contains 0.1% sodium metabisulphite and phenylmercuric borate (1:25,000) as preservative. When diluted with body fluids the aqueous insoluble analgesic base is deposited in a microcrystalline form. The slow absorption of this deposit is believed to be responsible for the long-acting analgesic properties of efocaine, but it is evident that such a compound might cause serious ill effects if deposited in delicate tissue.

Three examples of such complications have been reported from America by Shapiro and Norman (1953); in one patient intercostal nerve block in the thoracic region was followed by "transverse myelitis" causing permanent paraplegia. Three further examples have been reported by Brittingham *et al.* (1954); in all three, paravertebral block of several intercostal nerves with efocaine was followed by paraplegia. Two of these patients improved to some extent, but the third was permanently paralysed. Angerer *et al.* (1953) described another striking case in which paraplegia developed within a few minutes of the injection of efocaine into an intercostal nerve. This patient died, and the necropsy findings suggested that the spinal cord lesions were secondary to thrombophlebitis of an intercostal vein.

The present report deals with a patient in whom evidence of severe spinal cord damage occurred after the injection of efocaine into intercostal nerves for the prevention of post-operative pain after the reduction of a hiatal hernia.

Case Report

A married woman aged 50, who had complained of indigestion for many years, was found to have a sliding hernia of the stomach through the oesophageal hiatus of the diaphragm. In spite of medical treatment her condition deteriorated until she could take only fluids by mouth. Oesophagoscopy showed superficial ulceration of the lower oesophagus adjacent to the herniated gastric mucosa.

On January 1, 1953, left lateral thoracotomy was performed under general anaesthesia with thiopentone, D-tubocurarine, gas and oxygen. The patient lay in the right lateral position and the left seventh rib was resected. A local analgesic consisting of 1/2,000 amethocaine hydrochloride and 0.25% procaine was injected into the third, fourth, fifth, sixth, seventh, eighth, and ninth intercostal nerves, into the mediastinal tissues, and into the splanchnic nerves. The hernia was reduced and the diaphragm repaired without difficulty. Before closing the chest 1 ml. of efocaine was injected directly into each of the sixth, seventh, eighth, and ninth intercostal nerves at the angles of the ribs, where the nerves were clearly visible under the parietal pleura.

After returning to the ward the patient complained of numbness and paralysis of the legs. On January 2 she was found to have a flaccid paralysis of the lower trunk and leg muscles with complete sensory loss from the seventh dorsal dermatome downwards. Retention of urine and incontinence of faeces were present. On January 3 the C.S.F. contained 13 polymorphonuclear leucocytes per ml. and 950 mg. of protein per 100 ml., but there was no evidence of block on jugular compression. During the next three weeks her neurological condition did not change, but the C.S.F. returned slowly towards normal. On January 9 the C.S.F. protein value was 788 mg. per 100 ml. and on January 15 it had fallen to 435 mg.

The glucose and chloride content of the C.S.F. remained normal throughout. The C.S.F. Wassermann reaction was negative.

The thoracotomy wound healed normally and the digestive symptoms disappeared. A post-operative barium swallow showed complete reduction of the hernia and a normally functioning cardia. On January 24 the patient was transferred to a neurological unit for long-term rehabilitation.

On admission to the neurological unit some three weeks after operation the patient was found to have complete loss of spinal cord function from the seventh dorsal segment downwards. As she had complained of shoulder and trunk pains prior to operation the possibility of coincidental spinal cord compression was considered. A lumbar puncture on February 3 revealed the spinal fluid to be under a pressure of 110 mm. of water, with a rapid rise and fall of pressure on bilateral jugular compression. The fluid contained 3 cells (2 mononuclear and 1 polymorphonuclear), 100 mg. of protein per 100 ml., and an increased amount of globulin (Nonne–Apelt and Pandy). Radiographs of the spine showed no abnormalities apart from a minimal degree of osteophytosis in the mid-dorsal region, and a myelographic examination was within normal limits.

The usual measures for the long-term treatment of a spinal paraplegic subject were instituted. During the succeeding nine months there was never at any time evidence of returning spinal cord function. There remained complete absence of sphincter control, necessitating the regular administration of enemata and the maintenance of an indwelling vesical catheter. At the time of admission a small sacral bedsore involving skin and subcutaneous tissue was already present. This took many months to heal, and, despite the greatest possible care, it was impossible to prevent the development of similar lesions over the femoral trochanters. These later-developing lesions proved most resistant to treatment, so that at the end of the nine months' observation period they were still incompletely healed.

The patient was much troubled by persisting sensations of burning and "tightening" in her legs and lower abdomen, in addition to hallucinations of movements of her toes. These symptoms varied considerably in intensity from time to time and proved difficult to analyse, since they appeared to be dependent upon factors of both physical and psychogenic origin. Their response to the simpler analgesics was also variable, but at no time did they seem to become intolerable to the patient. On October 7 the spinal fluid was found to be normal in all respects, but in view of the extensive motor paralysis it was not possible to rehabilitate the patient beyond the state of a wheelchair existence, despite the application of appropriate leg splints. A final neurological examination confirmed that there was no objective evidence of spinal motor, sensory, or reflex function from the seventh dorsal segment downwards, a moderate degree of wasting of the legs having occurred by this time.

Discussion

This case emphasizes the possible catastrophic effects of the injection of a long-acting analgesic such as efocaine. It is conceivable that the drug passed along the perineural

sheath of one of the intercostal nerves, but the very high C.S.F. protein figures and the complete lack of recovery of reflex function below the level of the lesion suggest that extensive necrosis of the spinal cord occurred. Such widespread damage cannot reasonably be attributed to the small amount of efocaine which could have entered the spinal cord via the perineural sheath.

The clinical picture and C.S.F. changes can be explained on the basis of necrosis through interference with the blood supply of the spinal cord. The injection of efocaine close to an intercostal vein might have produced thrombosis which spread into the spinal cord and caused intramedullary thrombosis with necrosis. This view is supported by the necropsy findings in the patient reported by Angerer *et al.* (1953). Forty-four hours after the injection of efocaine they found that the intercostal vein immediately beneath the needle puncture was acutely inflamed and filled with recent thrombus. The spinal cord itself showed extensive necrosis, with evidence of acute inflammation.

The mode of action of efocaine has been reinvestigated by Mannheimer *et al.* (1954), and they have shown that the substance produces necrosis of both nerve and muscle of similar severity to that caused by the injection of alcohol and phenol. These findings, together with the published reports of gross neurological damage, lead to the conclusion that the clinical use of efocaine is no longer justifiable.

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Medical Memoranda

Long Survival in Renal Carcinoma

There are many gaps in our knowledge of the natural life history of malignant tumours, and renal cancer seems to be particularly unpredictable. In the patient we are here reporting, at least a quarter of a century elapsed before the disease caused death, and treatment was refused for a decade after the tumour was clinically apparent.

CASE REPORT

In 1930 a Jewish business man, aged 31, began to experience pain in the left flank and haematuria. The pain was episodic until 1934, when its severity so increased that he sought admission to hospital. A mass was then discovered in relation to the left kidney, of such a size that it caused obvious deformity of the stomach on radiological examination.

Surgical treatment was strongly urged, but the patient stubbornly refused to submit to operation until 1943. The operation disclosed a rounded tumour which replaced the lower pole of the kidney and was "much larger than the renal tissue proper." There was no involvement of the renal vein, or any evidence of metastases. Nephrectomy was carried out.

Pathological examination of the tumour by the late Colonel Harvey showed the tumour to be a glandular carcinoma (hypernephroma) of clear cell type. Its structure was unusually glandular, and of the small alveolar and tubular type rather than the larger and more cellular masses more common in this tumour. There was considerable polymorphism of the cell nuclei, suggestive of degenerative forms. Though mitotic activity was not recognized, the tumour had spread into the fibrous tissue separating the growth from the kidney. In some areas haemorrhage and necrosis were marked.

The patient remained relatively well until 1949, when he began to complain of vague abdominal discomfort. Sundry investigations were negative; but in 1952, when he came under our joint care, there was a mass in the left flank and some enlargement of the liver. Barium enema revealed a filling defect suggestive of extrinsic pressure in the descending colon, and a radiograph of the chest showed a rounded opacity in the right mid-zone. As much for diagnostic as therapeutic reasons, he was advised to undergo laparotomy.

At operation extensive malignant disease was found throughout the abdominal cavity, including a large fixed mass involving the descending colon and the adjacent part of the posterior abdominal wall. Numerous secondary growths were present in the liver, including a massive growth in the left lobe. It was found practicable to remove the pericolonic tissue and so relieve the obvious obstruction.

Histological examination showed the tissue to be metastatic hypernephroma. There was a remarkably good immediate recovery, and he was able to return to the business he had conducted so successfully throughout the years; thereafter his condition deteriorated; but in spite of the extensive metastases he survived for another two years, and died in September, 1954.

COMMENT

It is notoriously difficult to forecast the expectation of life in patients with renal tumours. Herbut (1952) has stated that symptoms and signs may be prolonged up to 35 years; and Griffiths and Thackray (1949) reported a 10-year survival rate of 21% after nephrectomy. The "best" American figures—those of Priestley (1939) at the Mayo Clinic—record a 10-year survival in 27.3% of 395 cases. Nevertheless, survival for 25 years despite the well-substantiated existence of renal carcinoma, as in the present case, seems to us most exceptional. Possibly the phenomenon was thrown into sharper relief by a number of contemporary cases in which the course was very rapid.

The corollary is obvious—that great caution must be exercised in venturing a prognosis in renal tumours, both with and without operation, and that even greater caution is needed when claims are made for the efficacy of treatment.

We are indebted to Dr. Alister Matheson for letting us have access to his careful records regarding this patient.

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Case of Bilateral Calcification of the Breasts

The deposition of calcium in the soft tissues of aged subjects is not uncommon, particularly in those parts where fibrous tissue normally predominates. In the breast, fibrous tissue is laid down in varying amounts after the menopause; only very rarely, however, does it go on to calcification so extensive as to be detectable both clinically and radiologically. The following is a case discovered accidentally shortly before the patient's death.

CASE RECORD

A woman aged 85 was admitted to hospital with a three-weeks history of pain in the left groin. Her private practitioner suspected the presence of a fatigue fracture of the neck of the left femur, no history of trauma being elicited. This was confirmed radiologically. Examination of the

breasts to exclude a primary malignant tumour revealed hard craggy mobile masses in the lower and outer quadrants of both breasts. The skin overlying them was normal, and no glands were palpable in the axillae or the supraclavicular fossae. Despite the remarkable hardness of the tumours, they were thought to be the result of fibro-adenosis. A routine chest *x*-ray examination revealed no intrathoracic abnormality, but the lower and outer quadrants of both breasts were found to be involved by extensive calcium deposits.

The patient underwent pinning of her femur, but succumbed to a hypostatic pneumonia ten days later. Specimens of her breast tissue were obtained at necropsy. The sections showed that the breasts had been practically replaced by fibrous tissue; large calcium deposits were irregularly scattered throughout the portions clinically involved.

COMMENT

It is unlikely that the breasts had previously been affected by fibro-adenosis; if they had, no remnant of such a condition was evident on microscopy. Such symmetry as was displayed here is, in any case, unusual. This symmetry may, however, be the clue to the aetiology of this condition. The pendulous unsupported breasts weigh heavily on the fibrous tissue, as they rotate downwards and outwards in the normal subject. Prolonged stresses and strains occurring in an abnormally fibrous breast are likely to exert their maximum effect on the lower and outer quadrant. Elsewhere in the body, fibrous tissue subjected to chronic stress not infrequently undergoes calcification; and it may be that a similar mechanism is responsible for the interesting distribution of calcium deposits, of which the above is an example.

My thanks are due to Mr. E. Chitty for permission to publish.

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Varicella with Neurological Complications in an Adult

Although chicken-pox is so common, involvement of the nervous system is extremely rare. In a study of 2,534 patients with varicella, Bullowa and Wishick (1935) found five cases of encephalitis and three cases of meningitis. Of the 108 cases with neurological complications described in the literature, in only eight was the patient over the age of 20 years, and about 90% were in the first decade of life.

CASE REPORT

An unmarried cashier aged 21 was admitted to hospital in September, 1952, with a severe attack of varicella, the rash of which had appeared almost three weeks previously. About a week after the onset of the illness she began to vomit once or twice a day, and continued to do so for two weeks. Twelve days after she had first noticed the rash she found that she was seeing double and that she had to close one eye in order to see clearly. Her past history was irrelevant. She had been vaccinated in infancy.

On admission she did not look unduly ill. She was co-operative and mentally clear. Her temperature was 101° F. (38.3° C.). She had a profuse rash on the trunk and limbs and to a less degree on the face. The lesions had a typical centripetal distribution and were mainly in the scab stage, but there were some pustules. There had been obvious haemorrhages into the more recent lesions.

Examination of her nervous system revealed no neck or back stiffness. Her pupils were equal and regular and reacted to light and on accommodation, but she was unable to abduct her right eye beyond the central position, and on looking to the right she had diplopia, the false image being projected to the right of, and level with, the true image. All other movements of the right eye and all movements of the left eye were normal; other cranial nerves and the disks and retinae were normal; tendon reflexes in the upper limbs were present and equal on the two sides; abdominal reflexes were present. The knee- and ankle-jerks were absent in both legs; plantar reflexes were flexor. Sensation to light touch, pain, heat and cold, vibration, and posture was normal. A coarse tremor of the outstretched hands, more marked on the right than on the left, was noticeable, but no intention tremor was present and there was normal co-ordination of movements in all limbs; no muscle weakness or wasting was found. There were no abnormal physical signs in any other system.

Investigations.—A full blood count was normal. The Wassermann reaction and Paul–Bunnell and Widal tests were negative. Blood culture was sterile. There were no pathogenic organisms in nose and throat, urine, or faeces. The C.S.F. on admission contained 110 mg. of protein per 100 ml.; leucocyte count, chlorides, and sugar were normal. The C.S.F. showed practically no change during the next five weeks, and even on discharge the protein was still 110 mg. per 100 ml.

Crystalline penicillin, 500,000 units six-hourly, was given, but she continued to have a swinging temperature, and on the fifth day of treatment the penicillin was discontinued and chloramphenicol, 500 mg. six-hourly, was given for seven days. Though the temperature subsided two days later, the impression was formed at the time that the improvement was coincidental and not in fact due to the treatment.

Towards the end of the second week in hospital it just became possible to elicit the knee- and ankle-jerks on reinforcement, and by the fifth week the reflexes were considered to be within normal limits; at about the same time the paresis of the right eye was beginning to show some improvement. Despite the improvement she was having mild attacks of depression with bouts of crying because she felt that her friends would laugh at her as she had a squint. She was discharged home on November 8.

When seen again two months later she complained of feeling nervous but was no longer depressed. She had occasional double vision and the right eye still showed some weakness of abduction; all other cranial nerves were normal and her tendon reflexes were present and equal. When last seen in October, 1953, she was considerably improved, had lost her nervousness, and had gained over 14 lb. (6.4 kg.) in weight. She had no diplopia and all movements of both eyes were full.

COMMENT

That nervous manifestations do not occur more often is surprising when it is considered that the causal organism of varicella is closely allied to, if not identical with, that of the neurotropic virus of herpes zoster. In the great majority of cases nervous complications occur between four and ten days after the appearance of the rash.

The C.S.F. findings have been recorded in only about 50% of published cases; the protein content was normal or slightly increased in 75%, but in the remainder there was a considerable increase; the leucocyte count was within the normal range in most cases.

The prognosis is good; about 90% of the patients recover. Residual defects are unusual, but are most common when ocular signs are the prominent or only manifestation of nervous system involvement.

I am indebted to Dr. Ernest Evans for his valuable criticism.

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Reviews

PTERIDINES

Ciba Foundation Symposium on Chemistry and Biology of Pteridines. Editors for the Ciba Foundation: G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Margaret P. Cameron, M.A., A.B.L.S. (Pp. 425+xiv. 42s.) London: J. and A. Churchill, Ltd. 1954.

When the late Sir Frederick Gowland Hopkins took up the study of butterfly pigments at the beginning of his career he believed that these substances might have metabolic significance. When he died in 1947 he had lived to see a tale unfolding which, although it still has much to reveal, has already borne witness to his prescience. Hopkins himself thought at first that the coloured substances he had extracted from butterflies were uric acid derivatives, and, since they appeared to be present in material voided from the rectum of lepidoptera, he inferred that "a normal excretory product subserves the purposes of ornament." It was not until 1940 that the difficulties of analysis and synthesis of these pigments were finally overcome, and one of the commonest, leucopterin, was shown to be not a purine but a pteridine derivative, pteridines being chemically related to the nucleus of riboflavine. Subsequently the structure and synthesis of many related insect pigments and other substances have been elucidated and some shown to have great metabolic importance.

In 1944 the name "folic acid" (Latin *folium*, leaf) was coined to described a growth factor from plant sources for *Streptococcus faecalis*, which later was found to be pteroylglutamic acid, a substance formed by the union of a pteridine with *p*-aminobenzoic acid and glutamic acid. Before this, in 1940, Woods and Fildes had recognized that *p*-aminobenzoic acid must be of importance in cellular metabolism because of its ability to overcome the inhibition of bacterial growth which can be brought about by sulphonamide drugs. Since pteroylglutamic acid was first isolated many related substances have been obtained from natural sources. Some have more than one glutamic acid residue in the molecule, and a number have been recognized as growth factors for micro-organisms of various strains. Rhizopterin (from *Rhizopus nigrans*) has a most interesting chemical constitution—namely, $N_{(10)}$-formyl-pteroic acid, pteroic acid being the substance obtained by the removal of the glutamic acid residue from pteroylglutamic acid. The fact that rhizopterin possessed one carbon atom in a reactive side-chain—a formic acid residue—was of particular interest.

The organism *Leuconostoc citrovorum* will grow on a medium containing liver extract, but in 1948 research showed that the liver extract could be replaced by a single substance folinic acid ("leucovorin" or "citrovorum factor"). Folinic acid is another formyl derivative, being $N_{(5)}$-formyl-tetrahydropteroylglutamic acid. In the processes of metabolism *p*-aminobenzoic acid is almost certainly converted into a substance closely related to folinic acid, this postulated substance, coenzyme F, being concerned in processes of biosynthesis in which one-carbon-atom units are utilized. Such a coenzyme or coenzymes may be involved in the synthesis of methionine, serine, histidine, and possibly other amino-acids, as well as in the formation of purines and thymine. In such instances a single carbon atom is introduced into the molecule under the aegis of the coenzyme, this atom almost certainly originating in a formic acid residue of the type found in folinic acid. Although these processes have mostly been worked out in micro-organisms, there is every likelihood that they also apply in the main to higher animals. There is now good evidence that sulphonamides inhibit bacterial growth by preventing competitively the utilization of *p*-aminobenzoic acid for the production of folinic acid or related substances, which the bacteria themselves need.

Pteroylglutamic acid is effective in the treatment of various types of experimental anaemia, and is of value as an addition to vitamin B_{12} (cyanocobalamin) in the treatment of pernicious anaemia in man. Here the biosynthesis of nucleic acids, dependent as it is on that of purines and thymine, may rest on the presence of co-factors closely related to folinic acid.

Antagonists to pteroylglutamic acid have been synthesized in the laboratory, of which aminopterin (4-aminopteroylglutamic acid) is the best-known. This substance can induce death with anaemia and leucopenia in experimental animals, and has been used in the treatment of acute leukaemia in children. Although it does not cure leukaemia, it may bring about a remission and can therefore be of aid in the treatment of this disease. Aminopterin inhibits mitosis in mammalian cells, and this suggests the possibility that folic acid derivatives may be of widespread significance in cellular reproduction, a process in which the synthesis of nucleic acids is of course of prime importance. Xanthopterin, a pteridine derivative simpler than pteroylglutamic acid, is a yellow colouring matter found in butterfly wings and in the yellow bands of wasps. Its administration to mammals is followed by enlargement of the kidneys to many times their normal size. Xanthopterin apparently directly stimulates mitosis and cell division in the epithelium of the renal tubules.

It is clear that a colloquium on the chemistry and biology of pteridines is dealing with matters of wide and deep significance. The volume under review gives the proceedings of a small international conference on recent progress in the research of pteridines, held under the auspices of the Ciba Foundation. The symposium was divided into two parts, the first on chemistry under the chairmanship of Professor A. Albert, and the second on biological aspects under that of Dr. W. Jacobson. Some of the titles of the sections will illustrate the scope of the discussions. "Recent development in pteridine synthesis," "The pteridines of *Drosophila melanogaster*," "Sulphonamide derivatives of pteridines," "Metabolic relations between *p*-aminobenzoic acid and folic acid in micro-organisms," "The function of folic acid in the biosynthesis of purine and pyrimidine derivatives," "The effects of folic acid analogues on the growth and cell division of micro-organisms," "The mode of action of folic acid antagonists and the function of the *Leuconostoc citrovorum* factor," "Some aspects of disordered folic acid metabolism in man," "Occurrence of hepatic fibrosis in children with acute leukaemia treated with folic acid antagonists." The book is well edited and the accounts of the discussions after each of the papers are very readable. The width of the discussions which occur when biologists and chemists meet together with a common interest is well illustrated by a colloquium which ranges from insect pigments to diseases of man. Biochemistry knows no boundaries of species and type, and, although one would not have expected *a priori* that the study of insect pigments would be of benefit in human medicine, such is the simple but stirring truth.

F. G. YOUNG.

RENAL FUNCTION

Reflections on Renal Function. By James R. Robinson, M.D., Ph.D.(Cantab.). (Pp. 163; 17s. 6d.) Oxford: Blackwell Scientific Publications. 1954.

This small book is based on lectures given to Cambridge students reading for an honours degree in physiology, and we are glad that the author has been willing to share his reflections with a larger public. The result is eminently suitable for a variety of readers, for, although Dr. Robinson makes no concessions to popularity, he requires really nothing of his reader beyond a reasonable intelligence and a willingness to be interested, and indeed entertained, by his clear account of a fascinating subject, written as it is in most attractive English. It is not long enough to tire him, nor so short as to be a mere synopsis. The more advanced reader will find here a point of view as well as an exposition, together with enough references to make a useful, if not comprehensive, bibliography.

A brief quotation from the introduction will give a better impression of the style and scope of this work than a summary of its contents. "The kidneys may be regarded as organs which help to stabilize the internal environment of

the body and to keep it chemically distinct from its surroundings. The elimination of waste products is but one aspect of this much larger task. . . . The two main questions to be considered are, first, how the kidneys do what they do, and, secondly, how they know what to do, or more properly, how they are directed to do it. This second question is concerned with the kidney as one part of the body in relation to other parts, and is for that reason more complex. The simpler question of the mechanism of the kidney itself will be taken up first."

ROBERT PLATT.

RESPIRATORY TRACT IN INFLUENZA

The Histopathology of the Respiratory Tract in Human Influenza. By J. F. Ph. Hers, M.D. (Pp. 77; illustrated. 17.50 Dutch florins.) Leyden: H. E. Stenfert Kroese, N.V. 1955.

This monograph provides much-needed evidence concerning histological changes in the trachea, bronchi, and lungs in human influenza. It is the most detailed account yet to appear of correlated bacteriological and histological studies designed to elucidate the precise role played by the influenza virus in the various forms of fatal influenzal bronchitis and pneumonia. The author marshals evidence from patients who died from infection by bacteria such as *Haemophilus influenzae* and the pneumococcus but in whom influenza virus infection could not be demonstrated. The changes in other patients with combined virus and bacterial infection are then compared and are used to attempt an interpretation of the relative role of virus and bacteria in the production of the well-known necrotizing epithelial lesions of influenza-virus–staphylococcal pneumonia. The argument that the virus and not the bacterium is responsible for necrosis of the ciliated epithelium of the trachea and bronchi, which has formerly been advanced purely on the basis of animal work, is thus reinforced by human evidence. Although the number of patients thus studied is small, the studies are elaborate and the results convincing.

The book is easy to read and beautifully illustrated. It also contains some interesting comments on the lungs in measles and chicken-pox and a few histological preparations from material collected in the 1918 epidemic and preserved in Leyden ever since.

C. H. STUART-HARRIS.

REGIONAL ALLERGY OF NORTH AMERICA

Regional Allergy of the United States, Canada, Mexico, and Cuba. A Symposium of Thirty-nine Contributors. Edited by Max Samter, M.D., and Oren C. Durham. (Pp. 395+xvii; illustrated. 61s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1955.

As is stated in the preface to this book, "the shifting industrial pattern of the country has made camp followers out of large sections of the population," and thus allergists throughout the North American Continent are frequently asked by their patients what effects a transfer to a different region will have on their symptoms and what regions are the most free from the particular allergens to which the individual patient may be sensitive.

This volume, which is the joint effort of some thirty-nine contributors in different regions of the continent, answers these questions very fully. The pollen and mould season and counts in the different regions throughout the year are given in detail and the major allergenic factors present in each region described. A special appendix lists the Ragweed Pollen Indices for the chief districts throughout North America, and should be particularly useful.

This book will prove invaluable to all allergists in the Americas, and to allergists in this country whose patients are considering immigration or are making visits abroad. The amount of geographical and climatic information given about each region makes the book surprisingly readable and will be of interest to many readers other than allergists. The printing and production are of the excellence expected of this publisher.

C. J. C. BRITTON.

SURGERY OF PULMONARY TUBERCULOSIS

The Surgery of Pulmonary Tuberculosis. By James H. Forsee, A.B., B.S., M.D., F.A.C.S., F.A.C.P. (Pp. 208; illustrated. 48s.) London: Henry Kimpton. 1954.

An up-to-date monograph on the value of surgery in pulmonary tuberculosis is particularly welcome, since the treatment of the disease has undergone radical changes in the past few years. The introduction of chemotherapy and pulmonary excision are the two most striking advances and have caused a therapeutic revolution. The author is an enthusiastic supporter of both these principles, and is optimistic enough to feel that an accurate forecast can be made of the time required for treatment.

The book is divided into sections, starting with the patient and his disease and the general application of surgery to pulmonary tuberculosis. The individual operations and their techniques are then described, and finally an analysis is made of the surgical treatment. This last section is worked out in detail, and supports the author's contention that excision of an arrested or controlled disease focus is a safe and satisfactory procedure. The figures given for thoracoplasty between the years 1947 and 1952 show a 74% good result in over 300 patients, as opposed to a 91% good result in 400 cases of pulmonary excision over the same period.

It is unlikely that precise indications for the selection of patients suitable for surgery will be widely agreed upon, but Colonel Forsee has defined his own attitude quite clearly and has based his opinions on an extensive experience.

T. HOLMES SELLORS.

GYNAECOLOGY FOR STUDENTS AND G.Ps

Gynécologie. By Nicolas C. Louros. Translated from the Greek by Dr. Télémaque Nicoglou. (Pp. 404; illustrated. 5,500 fr.) Paris: Expansion Scientifique Française. 1955.

This is a French translation of a textbook on gynaecology for students and general practitioners written by Professor Louros of the University of Athens. Professor Louros is well known in this country, especially for his writing on obstetrics, so it is all the more interesting to learn his views on gynaecology. And it is amazing to see how many he is able to express within the compass of this comparatively small and copiously illustrated book. For its subject-matter is all-embracing; it includes sections on endocrinology and operative gynaecology, and recalls shades of the past by adding breast surgery (including plastic operations) to gynaecology.

It is inevitable that some subjects receive little more than a mention to whet the appetite, but, by and large, the accounts of pathology and treatment tally closely with those obtaining in this country. The illustrations invite particular attention; many are reproductions from the German and American literature, but some of the best are simple line-and-wash drawings by the author himself. The half-tone illustrations relieved by a single colour are often more effective than those in full colour, but the production as a whole has a finish which makes it attractive.

T. N. A. JEFFCOATE.

MODERN CYTOLOGY

General Cytology. By E. D. P. De Robertis, M.D., W. W. Nowinski, Ph.D., and Francisco A. Saez, Ph.D. Second edition. (Pp. 456+xiv; illustrated. 40s.) Philadelphia and London: W. B. Saunders Company. 1954.

The first edition of this book was published in Argentina in 1946. This, the second edition, is a greatly expanded version of the first and can justifiably claim to be a reliable and readable general account of modern cytology written for those who, having a basic knowledge of genetics and the physical sciences, would like to learn some of the potentialities of this rapidly expanding science and the methods whereby the submicroscopic organization and ultimate metabolism of the cell are investigated and correlated with its manifold functions.

The illustrations are of good quality and carefully selected, there are many clear diagrams, references are plentiful, and the volume is neither heavy nor cumbersome.

G. HADFIELD.

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ANAEMIA AND PROTEIN MALNUTRITION

Anaemia is a major medical problem among the natives of tropical countries and several factors contribute to it. Malaria, *Ancylostoma duodenale*, and many other parasitic and infectious agents may lead to anaemia, but malnutrition is probably the most important single factor. The dietary ingredients necessary for normal haemopoiesis are many and diverse, including iron, trace metals, vitamin B_{12}, folic acid, vitamin C, and sufficient protein of high biological value. Whereas anaemia in Britain, when due to a deficiency of any of these factors, is usually attributable to a lack of absorption of iron or B_{12}, in the Tropics insufficient dietary protein seems to be the principal cause, and Professor A. W. Woodruff shows this to be so in his Goulstonian Lectures for 1954, published in our opening pages this week.

Woodruff has now been able to study 45 Nigerian women suffering from anaemia associated with pregnancy, his report[1] on the first 25 cases in this series having been published in this *Journal* in 1951. This anaemia was normocytic in about half the cases, macrocytic and microcytic respectively in about one-quarter. Reticulocytes averaged about 4%, indicating a fair degree of marrow activity, which was confirmed by marrow studies. With two exceptions the picture was macronormoblastic. The exceptions, in which megaloblasts were found, were among the minority of cases which showed a histamine-fast achlorhydria. Despite the considerable variation in mean corpuscular volume, the red cells throughout this group of patients were characterized by their unusual thinness, which is best expressed as the ratio of the mean cell diameter to the mean corpuscular average thickness. The increased variation of red cell diameter in each individual as revealed by a Price-Jones curve was a further characteristic of importance. The significance of these various minutiae of red cell shape and size lies in their remarkable similarity to those established by G. Larsen[2] as characterizing the anaemia associated with hepatic disease; this concordance is enhanced by the fact that the liver and spleen are enlarged in two-thirds of these Nigerian cases. Further evidence of hepatic damage was obtained by biopsy, which showed fatty infiltration or excessive fibrosis in all the 42 subjects so studied, findings usually associated with deficiency of dietary protein. The low level of the serum albumin and the high level of serum globulin, especially its γ fraction, seen in most of these cases is a further feature usually found in subjects with chronic liver disease. Haematology, blood protein levels, and hepatic biopsy therefore all agree in associating the anaemia with hepatic injury of the kind that is found both clinically and experimentally in conjunction with dietary deficiency of lipotropic factors—which, in terms of practical dietetics, implies a deficiency of protein.

Owing to the curious custom in tropical Africa by which the relatives are responsible for the feeding of hospital patients a fairly accurate estimate of their everyday diet could be obtained. This revealed that, although the caloric intake was perhaps adequate for subjects confined to bed, the protein level of 36 g. per day was less than half that recommended for pregnant women in the League of Nations 1936 report on the physiological basis of nutrition.[3] At this level there can be no doubt that the patients were indeed suffering from protein insufficiency. The complete failure of the anaemia to respond to folic acid, B_{12}, or iron, and the gradual but unequivocal response to a daily supplement of 56–113 g. of casein, show moreover that it is to this insufficiency that the anaemia must be attributed. Further evidence pointing to protein deficiency as mainly responsible for the anaemia is obtained from a study of the similar condition prevalent in the same community among young children and non-pregnant adults. The details of 9 young children and 21 older children and adults that Woodruff has collected can leave little doubt that the anaemia of pregnancy which he studied is but a special example of the general anaemia common among people subsisting on a diet poor in protein.

Since, according to the figures given by Tristram,[4] nine of the ten essential amino-acids make up 61% of the haemoglobin molecule, it is not surprising that an adequate intake of protein of good quality is essential for the maintenance of a normal haemoglobin level. Diets deficient in one or more of the essential amino-acids soon cause anaemia in experimental animals. This has been shown in rats when supplied with a diet deficient only in lysine[5] or methionine.[6] Moreover, with methionine deficiency the marrow

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[9] —— —— ibid., 1951, **94**, 223.
[10] *British Medical Journal*, 1955, **1**, 1245.

picture was typically macronormoblastic and indistinguishable from that described by L. Wills,[7] Woodruff, and others in their cases of anaemia in the Tropics. Further, since haemoglobin contains so high a proportion of amino-acids which the body is incapable of synthesizing, the nature of the dietary protein is at least as important as its mere quantity. Whipple and his colleagues[8 9] have made a special study of this problem, using for the purpose dogs depleted of both protein and haemoglobin by repeated bleeding. They have found that the processes by which haemoglobin and plasma protein are restored do not run parallel: beef protein, for example, favours formation of haemoglobin, while egg protein favours formation of the plasma proteins. In view of Woodruff's encouraging therapeutic results with casein it is of interest that Whipple has found that this is a "superior protein as promoting new haemoglobin and plasma protein output," comparing favourably with liver and beef under experimental conditions. Vegetable protein, such as peanut meal and wheat gluten, was far less satisfactory, partly because it was unpalatable to the experimental animal. This in itself may be a reflection of its inadequacy, since it has been shown,[6] for example, that small supplements of methionine greatly improve the impaired appetites of rats on diets deficient in this amino-acid.

Anaemia in pregnant women is by no means confined to the Tropics, though in Europe and the U.S.A. it is rarely attributable to deficiency of dietary protein; the great majority of cases are of the iron-deficient type. The rarer macrocytic variety is usually megaloblastic, and, although resistant to B_{12}, it responds readily to folic acid, as Professor L. J. Witts and his colleagues[10] reported in last week's *Journal*. The speed with which these cases respond is in marked contrast to the very slow reaction of the protein-deficient group. As Woodruff rightly points out, the protein deficiency of his tropical patients may amount to hundreds of grammes, and, though haemoglobin synthesis ranks high among the priorities, much of this deficit must be made good before the haemoglobin response becomes adequate.

STERILIZING THE GUT

In recent years, and especially since 1952, there have been increasingly frequent reports of sudden and severe, often fatal, enterocolitis after surgical operations. The main facts seem to be clear. The increase in this syndrome has followed the widespread use of powerful antibacterial drugs; the surgical operations which it follows are abdominal operations in which pre-operative antibacterial treatment has been used; in most cases almost complete sterilization of the faeces has been achieved before and just after operation; in many cases staphylococci are the only or the predominant organisms subsequently isolated; and these staphylococci are found to be resistant to the drug which has been used in pre-operative medication. The disastrous nature of this syndrome has been emphasized in this and other journals more than once,[1 2 3] but a paper by Mr. B. J. Fowler (page 1313) describing three fatal cases once again draws attention to this serious sequel of modern surgical pre-operative technique.

The first of Fowler's cases, a woman of 68, after a course of penicillin and streptomycin which failed to control local sepsis, at first showed rapid improvement when given chloramphenicol. Yet three days later she vomited, had severe diarrhoea, and died ten days after operation. The second patient, a man of 35, had received succinylsulphathiazole and streptomycin, went into a state of collapse after developing diarrhoea, continued to deteriorate on treatment with erythromycin and chlortetracycline (aureomycin), and died on the third post-operative day. The third patient, a woman of 82, had had penicillin and streptomycin, developed vomiting and diarrhoea, and died on the fourth day after operation. From the intestinal contents of all three patients coagulase positive staphylococci resistant to penicillin and streptomycin were isolated after death.

There can be little serious doubt that in Fowler's cases, as in so many others previously described, the disastrous outcome was the result of the antibiotic "umbrella" used to cover the operation. Although oxytetracycline (terramycin) has often been singled out as a conspicuous cause of post-operative enterocolitis, this syndrome is no respecter of antibiotics, and Fowler's cases show that the combination of penicillin and streptomycin can be just as dangerous. Some surgeons now feel that the fashion of gut sterilization has gone too far and would agree with Fowler's plea for the use of the poorly absorbed sulphonamides. The recent great fall in the incidence of peritonitis after abdominal operations seems to have been in large part due to the sulphonamides, and the more complete sterilization of the gut achieved by the antibiotics has been of doubtful value to the surgeon, who has to weigh one risk against another. If the danger of peritonitis after abdominal operations can be shown to have become very small as a result of using poorly absorbed sulphonamides, there would seem to be little point in striving to eliminate that risk completely if the process of eliminating it results, as so often seems to happen,

[1] *British Medical Journal*, 1953, **1**, 1382.
[2] *Lancet*, 1953, **2**, 1245.
[3] *British Medical Journal*, 1954, **2**, 221.
[4] Ibid., 1955, **1**, 973.

in greatly increased risk of fatal enteritis. One of the first things that needs to be done is to obtain an accurate appraisal of the facts and from that an accurate estimate of the risks involved.

There are several other questions arising out of this post-operative syndrome which urgently demand an answer. One of the most important of these is the question of dosage. Mennie[4] has sensibly pointed out that the doses of the drugs used are often far greater than the dose claimed by the manufacturers to be effective and indicated by preliminary pharmacological tests. One of the great difficulties with new drugs is to determine the smallest dose which will be clinically effective in man, and to determine it quickly before excessive dosage throws a drug into undeserved ill-repute. Then there is the epidemiological aspect of this syndrome. It mainly occurs in institutions, since it is there that nearly all operations take place. It also naturally tends to occur in certain wards, particularly where there is one surgeon who specializes in certain abdominal operations. The part played by the staphylococcus in the syndrome, however, is still mysterious. The staphylococcus is not always the cause, and bacteriological investigations are often not done or are done too late. There is a strong inference, however, that where the staphylococcus fills the "bacteriological vacuum" produced by over-efficient sterilization of the gut the strain which multiplies in the gut is one which is already present in the environment and which was already drug-resistant when it reached the victim's alimentary tract. The use of a particular drug, in fact, has merely given the drug-resistant organism the chance for which it was waiting. If so, then careful epidemiological studies of staphylococcal types in surgical wards would be of great interest.

Finally, what can be done in the treatment and prevention of this condition? Some lives have been saved by the prompt administration of erythromycin, often the only drug to which these staphylococci will respond. But in many cases both specific and general methods of treatment are bound to fail, since the condition is an acute and fulminating one. It is conceivable that vitamin deficiency may play a part in the development of the condition, and it has been suggested that the liberal use of vitamins may help to prevent it. But convincing evidence of this is lacking, and for the present it seems wiser to rely on some of the methods of prevention that have already been discussed—smaller dosage of antibiotics or, perhaps better still, none at all, with a return to the use of poorly absorbed sulphonamides, and at the same time energetic measures to eliminate staphylococcal infection from surgical wards.

AN EPIDEMIOLOGICAL CENTENARY

The Section of Epidemiology of the Royal Society of Medicine marked the centenary of the publication of the 1855 edition of John Snow's work on cholera by holding a meeting at the London School of Hygiene, where the public health students had prepared an exhibition containing many interesting relics—an outstanding exhibit being a portrait in oils, not exhibited before, lent by a member of the Snow family. Professor J. M. Mackintosh was unfortunately unable to be present because of illness, but in a paper read for him he sketched the social background to Snow's work and told how the opposition of the water companies of the time delayed the universal recognition of his conclusions.

The president of the Section, Professor Bradford Hill, in his appreciation of Snow, pointed out that his reputation rested not upon the removal of the handle of the Broad Street pump—an event that could have had little effect on an already waning epidemic—but upon his theory of the mode of spread of cholera, built up by reasoning based upon innumerable careful observations. Snow did not merely demonstrate the part played by infected water in the dissemination of cholera: by studying the way in which the disease spread from person to person he was able to infer—thirty years before the discovery of the cholera vibrio—that it was caused by "some material which passes from the sick to the healthy and which has the property of increasing and multiplying in the systems of the persons it attacks"; that this material derives from the faeces and vomit of patients and is introduced into the alimentary tract by swallowing; and that "the morbid matter of cholera, having the property of reproducing its own kind, must necessarily have some sort of structure, most likely that of a cell." From this basis he proceeded to show the part that was played by sewage-infected water in furthering the spread of the disease.

Many present-day workers see Snow as one of the founders of modern epidemiology. W. H. Frost wrote in the introduction to the American reprint of Snow's work, "Epidemiology . . . is something more than the total of its established facts. It includes their orderly arrangement into chains of inference which extend more or less beyond the bounds of direct observation." Much of the evidence produced in epidemiological studies is circumstantial in character, but such evidence can often be quite convincing, particularly when the epidemiologist makes use of the modern statistical techniques which are the outstanding contribution of the twentieth century to his subject. To-day the epidemiologist sees his greatest challenge in the aetiology of the common killing diseases of middle and later life. In his task he is finding that the old method of arrangement of facts into chains of inference to formulate a hypothesis, followed by the use of other data to test the hypothesis, is still a rewarding method of investigation. Although his analytical techniques have a refinement that was impossible a century ago, his method of working is in the direct descent from John Snow.

CLINICAL THERMOMETERS

About 3½ million clinical thermometers are sold in Britain annually, and it would be surprising if an occasional one out of so many instruments did not fall below its purchaser's expectations. But how many do not show the accuracy required of them is problematical. Since they are commonly read to the nearest 0.2° F., their materials and manufacturer must conform to strict standards, and the intricacies of glass-blowing are such that these standards are not easily attained. No doubt the manufacturers are constantly checking samples of their products, but a recent American investigation suggests that some independent checking might be worth while in Britain. E. G. Dimond and M. H. Andrews[1] tested 465 thermometers—all in use at a large general hospital—against a standard thermometer of known accuracy. Of these 465 clinical instruments, 34 (7%) were exactly in accord with the standard, 7% showed variation of 1° F. or more from the standard, and about 78% varied by less than 0.5° F. The greatest error was 3.3° F. from the standard. Clearly the unreliability of a small proportion of these thermometers could lead to difficulties in, for example, the investigation of a case of supposed continued low-grade fever in a child or the notification of a case of puerperal pyrexia. In Britain the National Physical Laboratory tests some clinical thermometers, and marks with its monogram those that pass the test. Some thermometers, too, are manufactured in accordance with the limits of tolerance set by the British Standards Institution, a letter from whose technical director appears at page 1339, and some of these are included among the instruments tested by the N.P.L. The British Standard permits a maximum error of ±0.2° F. at and below 106° F. The N.P.L. and B.S.I. thermometers cost slightly more, and comprise only a minority of those in use. Whether the cheaper types are sufficiently accurate for clinical practice is something that might well be investigated.

[1] Dimond, E. G., and Andrews, M. H., *J. Amer. med. Ass.*, 1954, **156**, 125.

TENDON REPAIR

At the end of the first world war Sterling Bunnell[2] laid down the principles governing successful tendon surgery, but it required the second world war to produce a rapid acceleration in their application and the growth of surgical teams primarily interested in hand surgery. The fundamental principles governing tendon repair are two[3]: first, all tendon repair demands vascularization from adhesions to neighbouring tissues, since the tendon has no blood supply of its own; and, secondly, any adhesions in the digital tendon sheath will affect the function of the tendon adversely. It has taken forty years of work to strike a practical balance between these mutually antagonistic factors.

Before the importance of early treatment to the injured hand was appreciated, experience had to be gained from the results of treating late hand injuries. It was found that if a tendon was to function there must be no adhesions to it; but local repairs in the tendon sheath almost inevitably produced local adhesion. The procedure of grafting was then devised, in which the tendon graft was sutured at the base of the terminal phalanx, where its gliding movement was small and adhesions necessary for its attachment were minimal, and suture of the proximal portion was done in the palm outside the tendon sheath. Careful attention to the digital sheath and its pulleys is essential to avoid adhesions, and difficulties are encountered where the sheath is occupied by two tendons, the so-called "no-man's-land" between the distal palmar crease and the proximal interphalangeal crease. Here the pressure on the graft resulted in adhesions to the sheath or to its fellow tendon, either or both usually leaving the finger with flexor sublimis function only. It was soon recognized that an actively functioning flexor profundus alone was all that was required, and the sublimis tendons were sacrificed by removal. On this basis very satisfactory delayed repair was possible.

To avoid the necessity for this complicated technique and the time wasted by the patient, attention was naturally turned to the acute injury, and some measure of general agreement has been arrived at in treatment. Again there are two main factors to consider. First, the type of wound has an important bearing on treatment. Two types may be distinguished: the incised wound—often surgical in its tidiness but most unsurgical in its disregard for anatomy—in which primary repair is possible; and the crushing injury in which fractures, bursting of the tendon sheath, and loss of skin may occur and are inevitably followed by adhesions and which demands delayed repair. Secondly, there is the level of the wound to be considered. If it is in the wrist, then primary suture is aimed at, since secondary repair is very difficult here. Once again the sublimis tendons can be sacrificed if necessary. In the palm primary suture is usually satisfactory. In the tendon sheath distal to the proximal finger crease the profundus can be sutured with every chance of success if the wound is a clean incised one. In "no-man's-land," because of the difficulties encountered, it has been the habit of many surgeons[4] to leave the wound and do a delayed graft. The terrors of this area may be more imaginary than real, for Allen and his colleagues in Chicago are now excising the sublimis and carrying out primary repair in this area when the wound is clean. It is interesting to note that Professor R. F. Bogdanov, of Sverdlovsk in the U.S.S.R., writing in this issue on the subject (p. 1315), is also quite definite that repair in this area need not be secondary. Extensor tendons, being surrounded by mesotendon and paratendon, offer no difficulty in repair, and the same proportion of successful results as is claimed by Professor Bogdanov for primary suture would be expected in English-speaking countries. Comparison of figures is, however, difficult, since Professor Bogdanov's statistics are based on a regional classification, and the end-results are much more strongly influenced by the character of the wound than its position. It is obvious from his report that surgeons in Russia are prepared to exercise

[2] *Surg. Gynec. Obstet.*, 1918, **26**, 103.
[3] Mason, M. L., and Allen, H., *Ann. Surg.*, 1941, **113**, 424.
[4] Rank, B. K., and Wakefield, A. R., *Surgery of Repair as Applied to Hand Injuries*, 1953, p. 100, Edinburgh.

the patience and scrupulous attention which the precision surgery of the hand demands, and are developing that special experience of their craft which is essential for success and which justifies the segregation of hand injuries in special clinics.

ROYAL SOCIETY CONVERSAZIONE

In spite of the enormous grants nowadays poured by the Treasury and industry into scientific research, at least some scientists seem to be free still to carry out investigations that have no immediate bearing on man's affairs. They were fairly well represented once again at the Royal Society's Conversazione held on May 19, when exhibits intended to illustrate some of the more important lines of research were displayed at the Society's rooms off Piccadilly. The songs of birds and the music of the spheres (detected by radio-telescope), the hearing of whales and the spinning of spider's webs, were the subject of exhibits that did not seem to portend the immediate exploitation of man's environment. But not quite the same could be said of the animated diagram showing how a chain reaction works in a nuclear reactor.

Of special interest to medical men was an exhibit by Drs. Jean Hanson and H. E. Huxley (of London and Cambridge respectively) showing how striped muscle contracts. Two different types of protein filament lie alongside each other, partly overlapping. Contraction occurs when the filaments of one type slide along those of the other type, so that the two arrays come to overlap almost completely. Supply of adenosine triphosphate causes this movement, and it was demonstrated under the microscope. Cinematography was the basis of two exhibits. Drs. G. M. Ardran and F. H. Kemp (Nuffield Institute of Medical Research, Oxford) illustrated the swallowing mechanism by means of short *x*-ray cine films taken of subjects swallowing radio-opaque fluids. This technique has shown, among other things, that the soft palate closes down on to the back of the tongue to help form a bolus in the mouth just before swallowing, and that this is its main role rather than shutting off the nasal from the pharyngeal cavity. Apparently it is true too that some people, though very few, really can pour a glass of beer straight down their throats without any appreciable swallowing movements with the mouth. The use of high-speed cinematography in analysing fast movements in living creatures was demonstrated by Dr. D. A. McDonald (St. Bartholomew's Hospital). His film, taken at 1,000-2,000 frames per second, showed a cat righting itself in falling (successfully but not quite so expertly when blindfolded), the flow of blood through arteries in experimental animals, and human responses to a blow to the face—all with an infinitely lethargic motion that would have appealed to Marvell's coy mistress.

Human respiration came in for a surprising amount of attention. Drs. A. J. Buller and A. C. Dornhorst (St. Thomas's Hospital) translated into electrical wave patterns the sounds passing through the chest wall, thus providing a visual analysis of such time-honoured clinical signs as aegophany, amphoric breathing, and dullness. Dr. B. M. Wright (Pneumoconiosis Research Unit, Cardiff) showed a small meter for measuring the amount of air breathed by a man at work. The mechanism consists mostly of wrist-watch wheels, and the air drawn through it when it is fitted into a mask turns a dial to record the volume. It was originally developed to estimate the dust inhaled by miners. Mr. H. S. Wolff (National Institute for Medical Research) was also occupied with a flow-meter, though of a different kind. It measures the volume of air a person expires while working, and also takes a sample for subsequent analysis. The oxygen consumed in a variety of jobs—some of them strenuously athletic—can be measured with it; and it can be worn for many hours, allowing the wearer to drink and to smoke. For light relief the visitor could contemplate a curious optical illusion staged by Dr. R. A. Weale (Institute of Ophthalmology, London).

No demonstration of current research would be complete without those sub-atomic particles of biology, the viruses. Dr. Elinor McCloy (London School of Hygiene and Tropical Medicine) showed how prophage—a kind of derivative or incomplete phage—is thought to become attached to specific sites on the genetic apparatus of bacteria, thereby blocking the destructive effects of phage in those bacteria. Drs. R. E. F. Matthews and J. D. Smith (Cambridge) illustrated the chemotherapy of plant viruses with some synthesized compounds similar to, but not identical with, the natural bases of the virus nucleic acids. The virus particles incorporate these synthesized competitors, and their powers of infection are thereby inhibited. With any luck this work may ultimately be of great importance not only in the treatment of human virus diseases but in furthering our understanding of what distinguishes living organism from dead matter.

TOXIC EFFECTS OF COBALT

The benefit conferred by cobaltous chloride in the treatment of certain anaemias of childhood and in the anaemias associated with chronic infection, renal disease, and carcinomatosis has been discussed recently in these columns.[1] Side-effects appear to be uncommon and occur usually with doses in excess of 100 mg. daily. Anorexia, nausea, and vomiting can largely be prevented by administering enteric-coated tablets. Tinnitus, deafness, flushing of the face and extremities, and paraesthesiae have been reported.[2] Large doses in animals cause renal damage, but this hazard has not yet been encountered in man, even in patients with severe renal disease. Recently, however, Kriss and his colleagues[3] have reported a serious and unexpected toxic action on the thyroid; they found hypothyroidism with hyperplasia of the thyroid in five of their patients. Goitres developed during treatment, and tests of thyroid function, including radioactive iodine, showed reduction of normal activity. This goitrogenic action has since been confirmed in

[1] *British Medical Journal*, 1954, **2**, 1038.
[2] Gardner, F. H., *J. Lab. clin. Med.*, 1953, **41**, 56.
[3] *J. Amer. med. Ass.*, 1955, **157**, 117.
[4] Gairdner, D., *et al.*, *Lancet*, 1954, **2**, 1285.

Britain.[4] Recovery follows withdrawal of the drug, and it would be interesting to know whether thyroid function is invariably depressed in patients receiving cobalt.

Why cobalt should cause polycythaemia remains a mystery, though animal experiments suggest that the metal inhibits enzyme systems containing sulphydryl groups. Kriss *et al.* believe—and there is some support from Kirkwood's experiments[3]—that it has a similar inhibitory action on the tyrosine iodinase system in the thyroid. It seems likely that the drug is a poison rather than an essential element in erythropoiesis, and this should be borne in mind when treating patients. While it is reasonable to treat cases of chronic renal disease and of carcinomatosis with cobalt, administration of the drug to children should await further knowledge of its side-effects. Many would agree that its inclusion in proprietary preparations for the treatment of anaemia is unjustified. Though caution is necessary in therapy, the demonstration that cobalt is a goitrogenic agent may help to unravel the biochemistry of thyroid function.

CINERADIOGRAPHY

Cineradiography, the formation of *x*-ray pictures at the rate of 16 per second or faster, has nearly always been carried out by the indirect method of photographing a fluorescent screen image. Speeds of up to 100 frames per second have been possible. However, the work has often been limited by overheating of the *x*-ray tube, poor definition, and the high dose of radiation necessary. The combination of fast film (35 mm.) and fluorescent screens together with wide aperture lenses (f 1.0 to f 0.71), camera shutters preferably closed for only one-quarter of the cycle, and pulsed *x*-ray units leaves little room for improvement along these lines. The dose rate depends on the type of examination being performed, but an antero-posterior view of the heart requires a skin dose of the order of 0.1–0.3r per picture.

Recently several methods have been devised by which a considerably brighter image of the fluorescent picture may be obtained.[1 2 3] The method developed by Coltman[1] consists of an electron lens which uses a fluorescent screen as object and produces a luminous image reduced in size but greatly increased in brightness. The Westinghouse–Marconi[1] and Philips[4] image intensifiers are of this type. Cinematography of the reduced, intensified image can be performed if a suitable optical system is available. With an apparatus of this type the skin dose of radiation for an antero-posterior view of the heart is about 0.2–0.5r per 100 frames, and 1.2r per 100 frames for an abdomen. The definition at maximum intensification is limited by statistical fluctuation of the *x*-ray quanta, as predicted by Sturm and Morgan,[5] demonstrated by Ardran and Wyatt,[6 7] and described by Tol and Oosterkamp.[8] A compromise may have to be made between definition and amplification of brightness. Thus within limits the definition will depend on the dose of radiation used. The definition approaches that of conventional intensifying screen radiography as the dose of radiation approaches that used in screen radiography. The best possible definition is not always required when moving pictures are viewed by projection, and thus the radiation dose may be kept low. The definition obtained in cineradiography by means of the image intensifier may, with only 2–5% of the radiation dose, be as good as or better than the definition obtained with orthodox cine fluorography. At present the small field which can be examined (approximately 5 in. (12.5 cm.) in diameter) limits the usefulness of the apparatus, but it may be employed for studying the act of swallowing, selective angiocardiography, and movements of the duodenal cap. Image intensifiers covering larger fields are being developed.

In the future almost all cineradiography and much rapid serial work may well be carried out with image intensifiers, when these are available in a size which covers the part under examination. Now that the limit imposed by overheating the *x*-ray tube has been removed it must be remembered that, although the dose per picture can be exceedingly low, the total dose can rise to a dangerous amount if the cineradiographic examination is continued for a long period. Great care will still be necessary to avoid an excessive dose to the gonads when the abdomen and pelvis are examined by cineradiography.

[1] *Radiology*, 1948, **51**, 359.
[2] *Amer. J. Roentgenol.*, 1949, **62**, 617.
[3] Moon, R. J., *Science*, 1950, **112**, 389.
[4] van Alphen, P. M., Burger, G. C. E., Oosterkamp, W. J., Teves, M. C., and Tol, T., *Fortschr. Röntgenstr.*, 1952, **77**, 469.
[5] *Radiology*, 1951, **57**, 556.
[6] Demonstration at the Annual General Meeting of the British Institute of Radiology, November, 1953. London.
[7] *J. Physiol. (Lond.)*, 1954, **126**, 1P.
[8] *Nature, Lond.*, 1954, **174**, 397.

"SURGERY, GYNECOLOGY AND OBSTETRICS"

Surgery, Gynecology and Obstetrics comes high on the list of famous and successful medical journals. For fifty years now leading surgeons have contributed to it, and their colleagues all over the world have turned to it as a source of authoritative information. The high and, indeed, luxurious standard of presentation reflects the pride of the editors, publishers, and printers in their journal, which in this its golden jubilee year has temporarily dispensed with its familiar cover and appears handsomely dressed in blue and gold. In the first number of the year Dr. Loyal Davis, the present editor, describes how the journal came into being in 1905. It was so successful financially that it could pay for the meeting of the Clinical Congress of Surgeons in London in 1913. Following that meeting the American College of Surgeons was founded, and since 1935 the College has owned the journal, the earnings of which are used to further the educational purposes of the College. In an editorial also appearing in the first number for 1955 Dr. Sumner L. Koch, an associate editor of the journal, looks beyond the remarkable surgical advances of the last few decades. If, as in his view is entirely conceivable, the centre of activity of surgeons moves during the next half-century from the operating-room to the laboratories of physics and chemistry, *Surgery, Gynecology and Obstetrics* will be there to guide them, as it has in the past, through the intricacies of new and strange techniques.

EMERGENCIES IN GENERAL PRACTICE

POST-PARTUM MATERNAL COLLAPSE

BY

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For the purpose of this article it is proposed to limit discussion to those cases in which sudden collapse of the mother occurs within a few minutes or hours after delivery. Such a condition may arise at any time during pregnancy or during the puerperium, but the varieties most commonly encountered in practice occur mainly during the immediate post-partum period.

A full discussion of these conditions would involve a survey of all the general medical and surgical conditions, to say nothing of those of obstetrical origin, which can lead to sudden collapse or shock. Broadly, they can be divided into conditions directly due to pregnancy and childbirth—that is, to obstetrical conditions—and those due to general medical or surgical diseases which are acutely exacerbated by the process of labour.

Obstetrical Causes

The causes arising directly out of pregnancy and labour which may lead to post-partum collapse may be defined as follows.

Haemorrhage.—This must be regarded as the commonest and most important cause of post-partum collapse. Bleeding may come from the birth canal and be visible externally; the main causes are retained placenta, uterine inertia, and bleeding from lacerations of the genital tract. Internal haemorrhage may occur, the most frequent cause being rupture of the uterus; internal bleeding may also occur from rupture of a vessel in the broad ligament or tearing of the vaginal vault. Antepartum haemorrhage, whether of the accidental variety or due to placenta praevia, is apt to be followed by post-partum haemorrhage.

Trauma.—Surgical shock may result from a difficult delivery or may follow precipitate labour. Many obstetric operations, and especially difficult forceps delivery and craniotomy, may lead to maternal shock; the cause appears to be linked with the effect of traction on the broad ligaments. A similar effect is seen when shock follows an attempt to deliver the placenta by Credé's method. The dangers of forcible manipulation of the uterus cannot be overemphasized, and indeed Credé's method has now been entirely abandoned by many obstetricians, who feel that they prefer manual removal of the placenta as the safer procedure.

Acute Inversion of the Uterus.—This may result from trauma, but in many recorded instances the uterus has become inverted in the absence of any interference. Acute inversion may be complete, the uterine fundus protruding from the vulva and lying between the mother's thighs, or it may be partial so that the fundus is not visible. In either instance the mother collapses in a state of profound shock which is probably caused by traction on the broad ligaments.

Embolism.—Pulmonary embolism may occur from previous venous thrombosis in cases in which thrombophlebitis or phlebothrombosis has occurred during the latter part of pregnancy; in general, however, pulmonary embolism from this cause is commonest between the tenth and fourteenth days of the puerperium. In cases of cardiac disease thrombi in the heart itself may be displaced during labour. Amniotic fluid embolism is a somewhat obscure condition, but the presence of amniotic fluid in the mother's lungs has been demonstrated in cases of unexplained sudden death during or shortly after labour. Air embolism is recognized as an occasional happening in labour. It may occur at forceps delivery, during manual removal of the placenta, or during packing of the uterus. It is possible that a low-lying placenta may predispose to its occurrence.

Drugs.—Pituitary shock is well recognized as a cause of collapse in the recently delivered woman and is believed to be due to spasm of the coronary vessels. Two important points must be made in this connexion. The danger of shock results chiefly from repeated administration of posterior pituitary extracts for arrest of post-partum haemorrhage. For this reason many prefer not to use them but to rely on ergometrine, which does not carry this risk and is equally effective. Posterior pituitary extract is much more dangerous than injectio oxytocini (*B.P.*), as the latter contains mainly the oxytocic factor. Nevertheless, as no pure preparation of oxytocin exists as yet, all known preparations of oxytocin containing a small proportion of vasopressin, shock may follow the use of the oxytocic factor. Thus if pituitary extract is given in the post-partum period, oxytocin should be used, but only one injection should be given; it should be used intravenously only with the greatest caution and in a dose not exceeding two units, if indeed it is used at all. Sudden collapse may follow the administration of anaesthetics during labour; the recently delivered woman appears to be particularly susceptible to this. Recent reports of maternal deaths due to inhalation of vomit have received considerable notice, and it must always be remembered that the stomach empties slowly during labour. Chloroform is especially dangerous in causing collapse.

Toxaemia of Late Pregnancy.—An eclamptic convulsion may occur in the recently delivered mother, and in severe toxaemia cerebral haemorrhage may cause collapse with coma.

Nervous Influences.—There are many who believe that post-partum collapse rarely if ever occurs without a cause such as one of those already described. Occasional cases are, however, encountered where the mother goes into profound shock after a normal delivery and no apparent cause is found. Collapse may sometimes follow a psychological shock at the time of delivery. Such an occurrence is described in the First Book of Samuel, Chapter 4, where the death of Eli and the birth of Ichabod are described: "And his daughter in law, Phinehas' wife, was with child, near to be delivered: and when she heard the tidings that the ark of God was taken, and that her father in law and her husband were dead, she bowed herself and travailed; for her pains came upon her. And about the time of her death the women that stood by her said unto her, Fear not; for thou hast born a son. But she answered not, neither did she regard it."

In practice, post-partum collapse in the absence of shock or haemorrhage is very uncommon, and it should be a rule always to exclude all possible physical causes before ascribing it to nervous influences.

Non-Obstetrical Causes

In the majority of cases where the mother collapses suddenly after childbirth an obstetrical cause is responsible. Nevertheless there is a variety of non-obstetrical causes for such a catastrophe. The main group consists of cases of heart disease, especially mitral stenosis. The woman who is in incipient heart failure before the onset of labour may

collapse suddenly when the uterus empties. Here an overloading of the maternal circulation results from the sudden release of blood from the pelvic organs, and this may even be fatal. Other less common cardiovascular diseases include myocarditis, pericarditis, and pericardial effusion.

Rupture of a vital organ may occur, as, for example, the heart, spleen, pancreas, aorta, mesenteric vessels, bowel, or gall-bladder. Internal haemorrhage may occur from the lungs, stomach, or splenic veins. Cerebral haemorrhage sometimes occurs even in the absence of severe toxaemia. Uraemia may become manifest for the first time in the immediate post-partum period. Profound anaemia in pregnancy may become evident for the first time after delivery, especially if there has been loss of blood during labour.

Diagnosis

The practitioner who is called to a case where the mother has collapsed suddenly after delivery is faced with a grave situation demanding immediate action. There will be time only for a rapid survey of the situation, but this is well rewarded, as correct diagnosis is essential before treatment is begun.

A brief history is taken; this will include the history of past illnesses, with special reference to conditions such as heart disease and anaemia. The history of past pregnancies is important. Operations such as caesarean section, hysterotomy, and myomectomy may have left a potentially dangerous uterine scar. The history of the present pregnancy will include the presence of any abnormalities and the amount of antenatal care received. Important events include toxaemia, anaemia, breathlessness, varicose veins, or antepartum haemorrhage. The history of the labour is next taken, including the length of each stage, and of the actual delivery, whether normal, difficult, or precipitate. A note is made of all drugs, including anaesthetics, given during labour and of any untoward symptoms such as vomiting or pain in the chest or abdomen. The history of the third stage is very important and should include an account of all attempts, whether successful or not, to deliver the placenta. If the placenta is available it should be examined to ensure that it is complete.

A general examination of the mother follows. The skin and mucous membranes are inspected for pallor and sweating. The rate and volume of the pulse are noted and the blood pressure is recorded. A note is made of obvious symptoms such as dyspnoea, restlessness, or pain in the chest or abdomen. The heart and lungs are next examined; a churning sound in the heart is characteristic of air embolism. The lungs may show evidence of pulmonary oedema.

Examination of the abdomen follows; the uterine fundus is felt to see if it is firmly contracted and palpable per abdomen. Tenderness or rigidity may be felt in the abdominal wall or over the uterus itself. Free fluid may be detectable if there is intraperitoneal haemorrhage. The vulva is next inspected to see if blood is still being lost. A pelvic examination should follow but may be deferred if the placenta is still retained. Pelvic examination after removal or expulsion of the placenta may reveal a laceration of the cervix or vagina or an incomplete inversion of the uterus.

The clinical signs of shock and haemorrhage are very similar. The patient is pale, sweating, restless, and anxious, the pulse is soft, and its rate rapid, often up to 150 a minute. The blood pressure falls, the systolic pressure falling more in proportion than the diastolic.

Prevention

Prevention of post-partum collapse begins in the antenatal period, when abnormalities such as toxaemia, anaemia, heart disease, and thrombophlebitis may be detected and treated. Disproportion, even in multiparae, must be excluded and potentially dangerous conditions such as multiple pregnancy and malpresentation diagnosed. The choosing of cases for home delivery is important: all cases with a previous history of grave disease and cases of multiple pregnancy, of malpresentation and of suspected disproportion are safest in hospital, where there are facilities for any emergency treatment that may become necessary.

During labour the emphasis must above all be on avoiding trauma and haemorrhage. Caesarean section has become so safe that it is to be preferred to difficult delivery, and it is now used without hesitation in many conditions. Few would condone the old "difficult forceps" delivery with excessive traction on the maternal soft parts and foetal skull; forceps should rarely if ever be applied before full dilatation of the cervix. The danger of Credé's manœuvre for expulsion of the placenta cannot be overemphasized, and it is doubtless still responsible for much unnecessary obstetric shock. In fact its use should no longer be taught to medical students or pupil midwives except to stress its dangers. Care must be exercised in the use of all drugs during labour, two of the most dangerous being chloroform and posterior pituitary extract. Perineal sutures should be inserted under local analgesia.

A massive post-partum haemorrhage will demand immediate treatment. The slow, steady trickle is almost more dangerous in that it may go on unnoticed until the mother is in a grave condition. The amount of blood lost after delivery should be most carefully watched and action taken when the total reaches 20 oz. (568 ml.), if not before.

Treatment

The treatment adopted in the individual case of post-partum collapse will depend on the cause; in most cases haemorrhage or shock will be responsible, and their treatment is dealt with in some detail.

The treatment of post-partum haemorrhage may be outlined as follows. If the placenta has not been delivered the uterine fundus must be gently grasped and rubbed up until it contracts: ergometrine, 0.25 to 0.5 mg., is then given intravenously. A strong contraction will occur in about half a minute and an attempt may then be made to deliver the placenta by gentle fundal pressure. Excessive force must be avoided, as this will only increase existing shock. If the attempt fails preparations should be made for manual removal, and meanwhile haemorrhage will have been checked. It has been shown that shock tends to increase for as long as the placenta is retained. Anaesthesia for manual removal will depend on the circumstances; the ideal anaesthetic for this purpose is a small dose of thiopentone, provided the necessary equipment, which must include oxygen, is available. In an emergency, manual removal can be gently performed without anaesthesia, or with analgesia with gas and air or trichlorethylene ("trilene").

If bleeding occurs after complete expulsion of the placenta, ergometrine should immediately be given intravenously; intramuscular injection is apt to be less effective in the shocked patient. The uterus will contract and bimanual compression should be carried out until bleeding is arrested. This is best done by the external method; the uterus is lifted well up into the abdomen and held firmly between the two hands. The patient's legs should be straightened and the foot of the bed raised. If bleeding continues and the uterus is empty and well contracted, the blood may be coming from a laceration of the genital tract, and arrangements should be made to suture this as soon as possible. In domiciliary practice it may be necessary to pack the vagina firmly with gauze until such arrangements can be made.

All cases of serious haemorrhage require blood transfusion, and it is here that in domiciliary practice the obstetric flying-squad service has proved most valuable. Restorative measures must be carried out while awaiting the arrival of blood. The foot of the bed is raised and moderate but not excessive warmth applied to the patient's body. Morphine, ¼ gr. (16 mg.), is given if she is restless and anxious. Blood should be taken for cross-matching and intravenous therapy begun without delay. There is no substitute for blood in a case of haemorrhage, but it may be some time before transfusion can be given. In the interval, glucose saline, or,

better still, one of the plasma substitutes, may be given by intravenous drip. Every practitioner who conducts midwifery cases should include in his equipment a giving set and one or more bottles of plasma substitute.

Three satisfactory plasma substitutes are at present available: polyvidone ("plasmosan" consists of a 3.5% aqueous solution of polyvidone with electrolytes in the same proportion as in plasma), dextran, and improved preparations of gum acacia. Blood must be taken for cross-matching before administering plasma substitutes, as their effect on the red corpuscles may make subsequent matching of blood difficult.

Plasma substitutes are advantageous in the treatment of post-partum collapse in that they have a pressor effect, so that within a short time of commencing administration there is often a dramatic improvement, the blood pressure rising and the pulse rate falling. In cases in which the blood pressure remains persistently low a small dose, say 10 mg., of methylamphetamine hydrochloride may be added to the drip, but this drug should be used with caution and in the minimal dose.

As a general principle, where there has been haemorrhage the amount of blood lost should be replaced by transfusion, but care must be taken not to overload the circulation, and the actual amount given will depend on the response to treatment.

When no improvement follows the arrest of external haemorrhage and adequate restorative treatment, including blood transfusion, internal haemorrhage must be suspected and the situation is grave. Immediate laparotomy is likely to offer the only chance of saving the patient's life, and arrangements for this, including removal to hospital if necessary, must be undertaken without delay.

Cases are now being described of post-partum haemorrhage due to afibrinogenaemia; they usually follow accidental antepartum haemorrhage. Steady and continuous loss of blood occurs after delivery, and if the blood is examined in a test-tube it is found that normal clotting is not occurring. The treatment of such cases is to give fibrinogen, but supplies of this substance are not as yet easily available. Bottled blood is useless as it contains little fibrinogen, but fresh blood or reconstituted dried plasma may be given if fibrinogen is not obtainable.

Oxygen is invaluable in all cases of shock and collapse, and should be given in high concentration, preferably with a special oxygen mask.

In treating shock in the absence of haemorrhage the same general principles apply, except that blood should not be given; general restorative measures should include moderate warmth, morphine for restlessness, oxygen, and intravenous infusion of a plasma substitute, with a small dose of methylamphetamine hydrochloride when the blood pressure remains low.

Acute inversion of the uterus may be responsible for unexplained shock; incomplete inversion may not be diagnosed without vaginal examination. The patient is likely to show profound shock, and, in addition, there may be haemorrhage. Restorative treatment should be begun at once. Replacement of the uterus may be undertaken by O'Sullivan's method. If the placenta is still attached to the uterus it is gently peeled off; the uterine fundus is replaced by giving a hot douche under pressure, while occluding the vaginal orifice with the forearm. This simple method has proved its value in many recorded cases.

In cases of embolism little can be done except to give oxygen; intravenous therapy is best avoided owing to the risk of overloading the already embarrassed heart. In the cases of collapse due to the rarer conditions treatment must be applied according to the cause, and accurate diagnosis becomes of the utmost importance.

Conclusion

Post-partum collapse is most frequently the result of haemorrhage or shock, and these still rank high among causes of maternal mortality. Their prevention and prompt treatment can save many lives. The contributions made by the National Blood Transfusion Service and the obstetric flying squads have done much to reduce maternal mortality to its present low level.

Next article on Emergencies in General Practice.—"Acute Hepatic Failure," by Dr. Sheila Sherlock.

Refresher Course Book.—Copies of the second volume of collected articles from the Refresher Course for General Practitioners are still available at 25s. (postage 1s.) each. The first volume is now sold out.

Clinical Pathology Book.—"Clinical Pathology in General Practice," a collection of 39 articles on clinical pathology that appeared in the *Journal* as part of the Refresher Course for General Practitioners, is now available, price 21s. (postage 9d.).

Both these volumes are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1, or through any bookseller.

JUBILEE OF SHEFFIELD UNIVERSITY

The University of Sheffield, with its 2,000 full-time students and 300 full-time staff, is engaged in a session-long celebration of its jubilee. The celebrations began last October with a visit by the Queen, were continued during the month of April in a series of "open days," when the public visited the departments, including the 13 departments of medicine, and they reach their climax on May 31 with a cathedral service and a little later with an honorary degree congregation. It was on May 31, 1905, that the royal charter was brought to the city, escorted from the station, we are told, by a procession of thirty carriages decorated with college colours.

The School of Medicine

Sheffield University grew out of three institutions, the oldest of which was the Medical School, founded in 1828. This was known earlier as the Medical Institution, but by 1868 it had become the Sheffield School of Medicine, having passed through many vicissitudes and perils, but gradually altering its character from an old school of anatomy concerned with apprentice assistants to that proper to a medical faculty. The greatest of its builders was Arthur John Hall (1866–1951), who joined the staff in 1889 and became eventually a legendary figure in the university. Another name which appears in the early records is Christopher Addison, who was professor of anatomy at Sheffield from 1897 to 1901. In the year that Addison came to Sheffield, University College (1897–1905) was founded, the Medical School joining with two institutions for arts and science and technology. The movement for higher education in Sheffield had been started by a group of great industrialists—Mark Firth, the Master Cutler, after whom the present Firth Hall is named, Henry Stephenson, and Frederick Thomas Mappin, all of whom belonged to the mid-Victorian era and established Firth College as an embryo university in which research in relation to local industries was specially developed. The Medical School came into the set-up not as a poor relation, as had been feared at one time, but as an equal partner, though it is true that, left on its own, the Medical School could hardly have developed into a university.

In 1905 King Edward VII opened the new university buildings on Western Bank, which meant for the medical departments far more satisfactory accommodation than they had had hitherto in their cramped quarters in the centre of the city. The first decade of this century saw the rise of a number of new universities. Leeds had been incorporated the previous year, Liverpool the year before that. The steel metropolis was in no way behind in the acclaim with which the creation of its university was greeted. At its

first conferment of degrees the awards, honorary and other, were so numerous as to move a local rhymester :

> "Oh, why this face of woe?" I asked a wight,
> With whom I talked awhile on yesternight—
> Said he, "I am the only man in town
> Who hasn't got a Doctor's hood and gown."

Sheffield and the B.M.A.

It was shortly after the establishment of the university that the British Medical Association held its annual meeting in Sheffield, when fifteen further honorary degrees were conferred on distinguished medical men, among them the president of the Association, Simeon Snell. There had been two previous annual meetings in Sheffield, one in 1876, when the president was Martin de Bartolomé, for many years president of the Medical School and leader of the profession in Sheffield, and the other in 1846, when the president was Dr. F. C. Favell, one of the eleven proprietors of the then Sheffield Medical Institution. Many famous names in medicine have been associated with the more recent history of the university—J. B. Leathes, professor of physiology, 1919–33; Edward Mellanby, professor of pharmacology 1920–34, whose appointment was the first to be made more for research than for teaching; and Howard Florey, professor of pathology 1931–5, who was later to make his name for his work on penicillin. In 1946 came the appointment of the first full-time professor of medicine, the present holder of the chair, Dr. C. H. Stuart-Harris.

The jubilee of the university is commemorated in a handsome and massive volume, *The Story of a Modern University*,[1] very closely documented, excellently illustrated, and altogether worthy of the occasion. It is the work of Dr. Arthur W. Chapman, the registrar of the university since 1944. It prints as a foreword a noble passage spoken by John Masefield at the inauguration of the late Earl of Harewood as Chancellor of the University nine years ago:

> "In these days of broken frontiers and collapsing values, when the dams are down and the floods are making misery . . . wherever a University stands, it stands and shines; wherever it exists, the free minds of men, urged on to full and fair inquiry, may still bring wisdom into human affairs."

Reports of Societies

PSYCHOLOGICAL FACTORS IN EDUCATIONAL DISABILITY

The Section of Psychiatry of the Royal Society of Medicine discussed "Psychological Factors in Educational Disability" at its annual general meeting on May 10, with Dr. W. MAYER-GROSS, president of the Section, in the chair.

Dr. D. RUSSELL DAVIS and Dr. NORMA KENT (Cambridge) described a study of intellectual development in schoolchildren with special reference to family background. They restricted themselves to those aspects of intellectual development that are measured by conventional intelligence tests. Their aim was to see in what way the home environment affects intelligence. Do the degree and character of a child's intelligence at a given age depend on his upbringing? They agreed that intelligence is due partly, but only partly, to genetical factors.

Home Influences

Ideally, they said, the effects of environment were best studied by comparing the abilities of pairs of identical twins where one of each pair had been brought up in a different family from the other—only such twins were rare. Another way was to study the intelligence of children transferred at different ages from their natural parents to foster-parents, and to see how far the children's I.Q.s correlated with those of the natural and adoptive parents. These correlations varied in degree according to the age of the children at adoption; when they were adopted at a few months old their intelligence later on was much closer to that of their foster-parents than of their natural parents. In assessing a child's upbringing, the factors most easily measured were probably not the most important. Notably in Iowa, attempts had been made to assess the "stimulation value" of the home, taking into account such things as the availability of toys, the participation of parents in play, the provision of space for play, and the quality of the talk and books in the home. Assessments made in this way correlated relatively highly with the intelligence of the children.

The rate of intellectual development was set not at birth but only gradually during the first few years of life. This was shown by the results of studies of children fostered at different ages and by studies on the "constancy" of I.Q.s. Thus correlations between tests and retests showed that I.Q.s were relatively constant during school years but were much less so at younger ages. Taking the correlation coefficients for test and retest after two years as measures of constancy, constancy was found to show a substantial increase between 2 and 6 years old. It was therefore in the children's circumstances during those years and earlier that one should look for the factors which affect the children's intelligence subsequently. Levy had shown that overprotected children were relatively good at reading and bad at arithmetic. Only children, and children first and last in order of birth, seemed to do well intellectually. Striking differences in the intelligence of the sibs in one family were common, and these might be attributed partly to difference in the ways in which the sibs had been brought up.

Discipline and Intelligence

Recent investigations in Cambridge had shown that there were consistent variations in the intelligence of schoolchildren according to the kind of discipline adopted by the parents. At lengthy interviews with the mothers, the kind of parental training was assessed, note being taken of the frequency, consistency, and generosity of rewards, etc., so that the child's upbringing was assessed as predominantly "normal," "demanding," "overanxious," or "unconcerned"; a demanding parent, for instance was one who set high standards, was inflexible in applying them, and gave poor rewards. One hundred and eighteen 8-year-old primary-school children had been given the Binet Scale (Form M), the W.I.S.C. "performance" subtests, and the Schonell graded word vocabulary test to measure reading age. Those who had demanding parents had a significantly higher mean I.Q. on the Binet than those from "normal" homes (124 compared with 110); their reading age was rather higher, but not significantly so. Of the 12 children with high I.Q.s (over 140) in the sample of 118, no fewer than 9 came from demanding homes. Children from "over-anxious" homes did significantly less well than the "normal" on the "performance" subtests (mean I.Q., 101 compared with 110), but did not differ significantly on the Binet Scale and reading test. Children with "unconcerned" parents showed a Binet I.Q. lower than that of the normal (97 compared with 110) and were particularly backward in reading—a pattern of test results shown by juvenile offenders. The conclusion was that the discipline in the home exerts a powerful influence on intellectual development, and that these findings have a bearing on the aetiology of mental defect.

Anxiety: Spur or Curb?

Mr. R. LYNN (Cambridge) spoke on "Emotional Factors in Reading Attainment" and concentrated on the effect of anxiety. There were two schools of thought: those like Schonell and Kanner who thought that when children were anxious for success their anxiety inhibited their efforts, and those who with Burt and Klein believed anxiety was a spur to effort and that the growth of reading skill was a form of defence against emotional upset. Mr. Lynn's survey was of 42 boys and 38 girls aged 7½ to 11 selected by their headmaster as good, poor, or average readers. Their reading age was assessed with Schonell's graded word vocabulary test,

[1] Oxford University Press, 50s. net.

and their tendency to anxiety by four informal interviews totalling three hours with the psychologist. At the interview they were asked informally six questions concerning personal anxieties, based on the Freudian view that the fear of loss of the mother was a source of anxiety, and six questions concerning impersonal anxieties. The questions in the first group included: "Have you ever been frightened your mother might die?", "Does scolding upset you?", "Are you easily hurt?", "Do you dislike being alone?" Those in the second group included questions about fear of thunder, of animals, of the dark, and tendency to nightmares. The results showed positive correlations between the reading age and affirmative replies to anxiety ($r = 0.33$ for personal group, $r = 0.24$ for impersonal group). The most striking individual case was a girl of 10½ with a reading age of 16½ and Binet I.Q. 146 who replied "yes" to four out of the first six questions and three out of the second six. She was discovered to come from a broken home with a timid, over-anxious mother. This supported the idea that anxiety favoured good school work, or perhaps it was that a central nervous system good at learning to read was also good at feeling anxiety.

Mr. Lynn went on to discuss anxiety as a socializing force, and to suggest that it might sometimes need redirecting rather than eliminating altogether, and this point was taken up in subsequent discussion when speakers suggested that neurotic anxiety was different from Lynn's questionary measure, and that the quantity of anxiety was important. A little might be good, a lot was bad. Other discussion turned on the relative value of questionary and interview, on the reliability of intelligence tests, on the exponential growth curve, which implied that a two-years span at three years old was not the same thing as two years at seven. Dr. DAVIS made it clear that in his results there was no correlation between parental I.Q. and the class of discipline in the home.

Constitutional Factors

Finally, Mr. GEORGE ETTLINGER read a paper by himself and Mr. C. V. Jackson (Institute of Neurology, London) on "Organic Factors in Developmental Dyslexia."

Difficulty in reading was commonly associated with certain factors which included anomalies of lateral preference, anomalies in the visual perception of apparent movement, minor E.E.G. abnormalities, anomalies of maturation of spatial and temporal perception, as well as indications of a specific genetical background. They had excluded from a group of 24 dyslexics referred to the National Hospital for Nervous Diseases at Queen Square 16 on account of the presence of frank neurological disorders or marked emotional or psychoneurotic features (which could be construed as primary to the dyslexia) or on account of insufficiently pronounced dyslexia. The remainder seemed to show marked reading disability without neurological signs and in association with better than average general intelligence. Half of these cases were, however, also retarded on visuo-constructive tests. Of special interest was the finding that only four cases were fully right-handed, and consistent unilateral hand, foot, and eye preferences were present in only one-third of this admittedly small group of cases. Moreover, some sinistral ancestry was reported in five out of the six cases in which relevant data were available, and a family history of dyslexia was established in one case. The results on the Jasper-Raney test of lateral dominance accorded with the view put forward by McFie that in many dyslexics normal dominance had not become fully established in either cerebral hemisphere. The present study, though insufficient in numbers for sure conclusions, emphasized the constitutional origin of specific dyslexia, which was best regarded as a selective failure of learning, directly due to defective maturation of those cerebral mechanisms underlying language and its development.

In the subsequent discussion it was suggested that many if not all of the cases of specific reading disability that were not secondary to mental defect could be regarded in this light (according to Dr. MAYER-CROSS 24% of Army recruits are backward in reading). Nor did such cases show any speech disorder or motor clumsiness, even of a minor kind. The speakers had no suggestion for their treatment.

Nova et Vetera

DAVID BRUCE (1855–1931)

Sir David Bruce, who was born in Melbourne of Scottish parents on May 29, 1855, received his medical education at Edinburgh. After qualification in 1881 and two years in general practice he joined the Army Medical Service. While on duty in Malta he investigated many cases of the obscure continued fever then prevalent on the island, and in 1886 he isolated from the spleen in fatal cases an organism, *Micrococcus melitensis*, which he proved was the cause of Malta fever.[1] It was later renamed *Brucella melitensis*.

Bruce left Malta in 1888, and after a teaching appointment at Netley he was posted to South Africa in 1894. Here his attention was directed to nagana, a disease causing many fatalities among horses and cattle. Within two months he was able to report[2] the discovery of an organism (later named *Trypanosoma brucei*) in the blood of infected animals. During the next two years Bruce and his wife elucidated the main facts as they are now known about trypanosomiasis and its transmitter, the tsetse fly. The Bruces were among those besieged in Ladysmith during the South African war, and served respectively as operating surgeon and theatre sister.

It was J. Everett Dutton[3] who in 1901 first recognized trypanosomes (*T. gambiense*) in the blood of humans suffering from sleeping sickness. In 1903 Bruce went to Uganda to supervise and control the Royal Society's Sleeping Sickness Commission. With D. N. Nabarro he showed that the tsetse fly was the vector.[4] Castellani, a member of the commission, had found trypanosomes in the cerebrospinal fluid in five cases of sleeping sickness a year previously[5] and had informed Bruce of the fact. Trypanosomiasis due to *T. brucei* did not affect man, but Bruce recognized the implications of Castellani's findings. He set up fly-feeding experiments, and by August, 1903, he had proved that sleeping sickness was caused by a trypanosome, that the vector was the tsetse fly, and that the disease could be transmitted by the bite of this insect.

Later work by Bruce included the demonstration of the source of infection of Malta fever in goat's milk, and research on the aetiology and control of trench fever and tetanus. He was knighted in 1908. A bibliography of his publications, together with appreciations of the man and his work, appears in the current *Journal of the R.A.M.C.* (April, 1955).

Bruce married in 1883 Mary Steele, a daughter of a general practitioner, and she assisted him in all his scientific work, both at home and abroad. He died in London on November 27, 1931, four days after Lady Bruce.

Sir Rickard Christophers has concluded a biography[6] of Bruce with the following discerning sketch of his character: "Bruce was a man of strong physique and forceful mind. . . . His approach to the problems which he undertook to solve was extraordinarily simple, logical, vigorous, and direct, and this was backed by a remarkable, seemingly intuitive, perception of the essential point for attack. In his personal relations, whilst he is said to have been somewhat reserved and self-contained, all agree as to his loyalty and integrity of mind and purpose."

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BRITISH ASSOCIATION OF PHYSICAL MEDICINE

ANNUAL MEETING IN LONDON

The annual meeting of the British Association of Physical Medicine was held at St. Thomas's Hospital, London, on April 22 and 23.

The first subject discussed was "The Use of Hydrocortisone by Local Injection," and Dr. J. H. CYRIAX drew attention to the great importance of accurate anatomical localization of soft-tissue lesions for the effective use of hydrocortisone. Dr. P. HUME KENDALL described results obtained at Guy's Hospital. In selected cases of rheumatoid arthritis it had been confirmed that the chief value of the hormone appeared to have been the production of a remission sufficient to permit the commencement of more active physiotherapy than would previously have been possible. In osteoarthritis hydrocortisone had been of use only in the early case or where symptoms had been aggravated by recent injury. In acute rotator cuff lesions of the shoulder results had been good, but the effect on the "frozen shoulder" was usually disappointing. Various soft-tissue lesions such as tennis and golfer's elbow, plantar fascitis, de Quervain's syndrome, and tenosynovitis had responded well. In acute traumatic articular effusions uncomplicated by serious bone or ligamentous injury the results were often dramatic, even in the presence of haemarthrosis, where hyaluronidase was combined with hydrocortisone after aspiration.

The Department of Physical Medicine

Opening a discussion on "The Department of Physical Medicine," Dr. W. S. TEGNER reviewed the evolution of the modern physical medicine department of a large hospital. Physical medicine had been and was still undergoing changes, and that necessitated fluidity in the make-up and organization of departments. Space and ease of access were important, and many architects still thought in terms of a rigid design incapable of adaptation. As regards staff, doctors, physiotherapists, technicians, and often nurses worked together, and there might be difficulties in integrating their various activities to secure efficiency. This also raised the question of the relationship of the physiotherapy school with the physical medicine department, and Dr. Tegner deplored attempts to use students as a form of cheap labour, particularly where this practice had prompted the opening of a school of physiotherapy. Beds and doctors in adequate numbers were required by physical medicine departments, since attendances and waiting-lists continued to grow all over the country.

Dr. W. A. FELL drew attention to the problems peculiar to physical medicine departments outside London and the bigger provincial centres, since over 25% of the patients might come from many miles away and have to spend a whole day away from home or work for the purpose of receiving one treatment. Some of those with even minor complaints found it impossible to travel the mile or so from home to the nearest point at which public transport was available. The only alternative in these cases was to use expensive hospital transport. At present it was necessary to treat patients in the central department, because only there could be found the requisite medical and technical staff and equipment. There was thus an overwhelming case for the provision of properly constituted peripheral clinics.

Disadvantages of the "Closed" Department

Dr. A. T. RICHARDSON said that the maintenance of closed physical medicine departments was indefensible for any reason, since it wasted the time of patients, doctors throughout the hospital, and physiotherapists, and prevented the general practitioner from having direct access to the physical medicine specialist. It might be argued that the closed system permitted a filtering of patients referred to physical medicine specialists, but surely they were the very people best fitted to reject cases for which there were no indications for treatment in the department. A great deal of time could be saved by a sound system of decentralization whereby a patient could go to the department with a written prescription—e.g., from the dermatologist for ultra-violet-light therapy, from the chest department for breathing exercises, or from the orthopaedic surgeon for post-operative exercises. To achieve real efficiency, however, the physical medicine specialist and the physiotherapy services must be used intelligently, and this in turn depended on the better training of students in this field of medicine.

Dr. Richardson included within the scope of physical medicine the diagnosis and treatment of the medical disorders of the locomotor system, the treatment of these and other disorders by physiotherapy, and medical rehabilitation. It was now considered that the M.R.C.P. or its equivalent was essential for the attainment of consultant status in physical medicine, in addition to considerable experience in the specialty and the possession of the Diploma in Physical Medicine. There were now a sufficient number of fully qualified registrars to ensure that future appointments to consultant grade would fulfil these criteria.

Dr. F. S. COOKSEY expressed his concern at the shortage of physiotherapists. Unless a lowering of the standards of training for physiotherapists was to be accepted (a suggestion firmly rejected by many later speakers) there would have to be a continual economy in the prescription of treatment. He made a plea for a firm integration of the medicine practised in the physical medicine department with other hospital services and in close association with the local authority services and general practitioners.

In the ensuing discussion a number of speakers mentioned the apparent ignorance of many members of the medical profession and of lay committees of the proper function of the qualified physical medicine specialist and his department.

Correspondence

Diversities of Sex

SIR,—Dr. C. N. Armstrong (*Journal*, May 14, p. 1173) has made a most graceful contribution to an important and difficult subject. He has given a simple practical classification of the diversities of sex, which in the past have been enshrouded in ambiguity. Few previous classifications have helped to simplify; most, owing to their complexity, have increased confusion.

I agree that there is no precise definition in law or medicine of what really constitutes male or female sex. Social laws demand it, but law and medicine, being exact and enlightened sciences, recognize the fact that there is often no clear-cut definition between the male and female. Sex perhaps, like most other things, is merely a question of relativity. Dr. Armstrong wisely emphasizes the difference between the genetic and the gonadal sex of the individual. Fortunately, in most people these correspond and there is no problem, but serious difficulties may arise when there is divergence between the genetic and gonadal sex and if there is added to this an imbalance of hormones. The subject then becomes extremely complex and a clear-cut definition of the sex is impossible. I believe, also, that the process of sexing by chromosomes is at present inexact and unreliable. This may be due to human errors and lack of experience in a new field. At present, I have under my care a patient whom I believe to be what Dr. Armstrong would describe as "a female pseudohermaphrodite." One authority on chromosomes called her a girl and another a boy. She is a girl, and has always been brought up as one, and will, I hope, always remain one.

It is of very great practical importance to make the right sex diagnosis in small babies soon after they are born, if possible, because they will soon have to be christened and a correct diagnosis will make life easier and more happy for them. However, if a patient of doubtful sex comes for treatment and advice in adult life, it is usually unwise to change the sex in which they have been reared and in which they usually wish to remain. I thoroughly

agree, however, that if the sex is obvious and the patient wishes to "change," being a transvestist and psychologically bizarre, it is most improper to accede to this. Moreover, the gonads should not be removed from any patient of doubtful sex in order to satisfy the patient, the surgeon, or the barrister. It may cause irreparable misery, and I expect Dr. Armstrong recognized this mistake in his Case 1, although he does not mention it. Everyone interested in this subject will remember Harold Chapple's[1] classical description of the really beautiful girl, with ardent amorous instincts and activities, who lost all her womanly beauty and charm, and then her happiness, when, against his sound advice, her testes were removed.—I am, etc.,

Leeds, 1. MICHAEL C. OLDFIELD.

REFERENCE

1 Chapple, H., *British Medical Journal*, 1937, **1**, 802.

"Half-minute" Thermometers

SIR,—In your issue of May 7 (p. 1158) Dr. Peter Gilbert drew attention to the unreliability of the conventional "half-minute" indication on clinical thermometers, and he asked whether it would not be possible for every thermometer to be supplied with a "certificate of time" as well as of accuracy.

Apart from the fact that the provision of such an additional certificate would involve extra cost for the manufacturer, it still would not overcome the difficulty that the time required for a particular thermometer to indicate the true temperature of a patient depends on a variety of factors outside the manufacturer's control. We are advised by medical authorities that the most important of these are: the initial temperature of the thermometer, the manner in which it is placed (and retained) in position, and the physical condition of the patient. Even to indicate a minimum time, such as three or five minutes, might well be misleading in some circumstances of use. It is expressly for these reasons that a time indication is not given on a British Standard clinical thermometer. Thermometers made in accordance with the provisions of British Standard 691 (which was revised last year) are classified as "quick," "medium," or "stubby," and each must be accompanied by an explanatory note drawing attention to the considerations mentioned above.

Although British Standard clinical thermometers are coming into increasingly wide use by the medical profession and hospital authorities, it is known that the advantages they provide for a very slight additional cost are still not appreciated by many people, and for that reason this Institution is shortly undertaking an information campaign to encourage the wider use of British Standard thermometers. The interest and help in this direction of professional people would be as welcome as it would obviously be valuable.—I am, etc.,

London, W.1. G. WESTON,
Technical Director,
British Standards Institution.

Niddah and Sterility

SIR,—Sir Ernest Kennaway (*Journal*, May 7, p. 1107) suggests that there is some doubt as to how often the law of Niddah (post-menstrual abstention from coitus) is observed to-day among Jewish patients. I would suggest that it is far more frequently observed than many people imagine and that in this infertility clinic it is a most important cause of sterility.

Where a woman has a short menstrual cycle, for example 23 days, she will ovulate about the ninth day. If, as often happens, she menstruates for eight days and then observes seven days' abstinence, the first coitus will not be until the 15th day—that is, when the ovum is presumably dead. Every year I meet with a number of cases of this type, which quite often have been subjected to considerable useless treatment for what is a very simple condition, once the knowledge of Niddah is kept in mind. The administration of oestrogen or sometimes testosterone at the onset of the period will postpone ovulation and enable such patients to have intercourse when the ovum is still alive. The fact that Niddah is such an important factor in my clinic suggests that it is observed by many other orthodox Jewish patients, and therefore may well be an important factor in cervical cancer, as Sir Ernest suggests. Certainly all those dealing with orthodox Jewish patients who are infertile should inquire about its observance.—I am, etc.,

Manchester, 8. BERNARD SANDLER.

Professional Secrecy

SIR,—My attention has been drawn to a communication, H.M.(55)46, from the Ministry of Health, dated May 10, 1955, addressed to regional hospital boards and hospital management committees concerning "Carnal Knowledge of Mental Defectives" (see *Journal*, page 1350). This memorandum describes the new procedure to be adopted when a certified mental defective is found to be pregnant, or there is reason to think that sexual intercourse has taken place. A previous memorandum on this subject advised that a report should be submitted to the Board of Control but that the local police should not be informed. The new memorandum repeats the advice of reporting the facts to the Board of Control, but reverses the advice on communication with the police. It states that "the Ministry is of opinion that it is desirable that in future such cases should be reported to the police not necessarily with a view to prosecution but to enable the police, in consultation with the medical superintendent, to decide what is the best course to take in all the circumstances." It concludes that medical superintendents should send reports to the local chief constable even where the offence has been committed in another police area.

The current policy of the Association concerning professional secrecy is expressed in the following terms: "It is a practitioner's obligation to observe strictly the rule of professional secrecy by refraining from disclosing voluntarily without the consent of the patient (save with statutory sanction) to any third party information which he has learnt in his professional relationship with the patient."

Unfortunately the advice now tendered by the Ministry of Health has apparently been prepared and issued without any prior consultation with the British Medical Association or any of the defence bodies who are materially interested in this matter for the protection of their members. Furthermore, reasons have not been advanced to justify the change of advice and the abrogation of the rule of professional secrecy in the case of mental defectives.

There may well be occasions when it would be fitting and proper for the police to intervene by the institution of legal proceedings against a suspected offender, and there may also be sound reasons in law for issuing the advice described above. The writer feels, however, that, before a change of this order is sponsored by official Governmental departments relating to an important ethical tenet, the least that the Association could expect would be a communication from the parties who propose an alteration, setting out their reasons and any legal sanction that might be invoked for their support. I hope that opportunity will be afforded in the near future for representatives of the Association and of the Ministry to meet to discuss the situation created by the issue of the memorandum.—I am, etc.,

London, W.C.1. ROBERT FORBES,
Chairman, Central Ethical Committee.

Reserpine in Treatment of Chronic Psychotics

SIR,—I was interested to read the paper by Dr. E. S. Foote entitled "Reserpine in Treatment of Chronic Psychotics" (*Journal*, May 14, p. 1192). Chronic psychotics have been under treatment here on similar doses of reserpine for the past five months, but preliminary results in a controlled series have been rather disappointing so far. The practice has been to leave the patients' routine unaltered, apart, of course, from the administration of the tablets and the daily blood-pressure readings, and this may possibly be a reason why our results have been less promising than Dr. Foote's.

With regard to side effects, I think it is worth reporting at this stage the case of a female patient who complained of feeling "faint and dizzy" on two occasions when climbing the ward stairs during the first three days of treatment

with reserpine (1½ mg. three times a day). She stated that she had never felt like it before, and, in spite of continuing with the same dose, has had no similar symptoms since. Her daily blood-pressure readings showed no significant alteration from her pre-treatment readings, but one cannot help feeling that these two incidents were the result of a temporary fairly profound fall in blood pressure associated with moderately large initial doses of reserpine. I therefore agree with Dr. Foote that the initial dose should not be more than 0.5 mg. three times a day, and this dose is now given here as a routine for the first four days of treatment. I was interested to read of Dr. Foote's report of oedema occurring in patients with no apparent organic cause, as I have also had one similar case and wondered if it might be the result of reserpine therapy.—I am, etc.,

Epsom. D. L. M. MCNEILL.

Agricultural Pesticides

SIR,—May I be permitted space to comment upon the remarks made by Mr. A. F. McK. Jackson (*Journal*, May 7, p. 1157) relating to aldrin and dieldrin? Shell Chemicals Limited has not issued any literature containing a statement to the effect that dieldrin has eight times the oral toxicity of D.D.T. to mammals, nor, to the best of my knowledge, is there any other authority to that effect. What they have said, however, is that these compounds have an insecticidal efficiency of some eight times that of D.D.T. against many insect species. Aldrin and dieldrin, in common with all other chlorinated hydrocarbon insecticides, can be absorbed through the intact skin, but there is no question of such absorption taking place through the soles of normal footwear in ordinary everyday use, as is suggested by your correspondent. No special measures, other than those recommended for handling insecticidal chemicals such as D.D.T., are required for the processing, mixing, or application of aldrin- and dieldrin-based products.

Since their introduction over five years ago no serious cases of intoxication by aldrin or dieldrin have occurred during manufacture, formulation, or application of tens of millions of pounds of the technical materials, despite the fact that in a number of cases normal precautions were flagrantly disregarded. This record is particularly notable in view of the fact that large quantities of these insecticides have been handled by totally unskilled labour in many of the under-developed areas of the world. In a few instances there have been suicide attempts using aldrin and dieldrin, but in spite of the fact that gross overdoses—in one case amounting to 25.6 mg. of aldrin per kg. of body weight—were taken orally, no case proved fatal and the patients recovered without sequelae.

The last thing I wish to suggest is that materials of this nature can be handled without taking due and proper precautions, but, provided such precautions are taken, I see no reason, on the evidence available, to be alarmist in regard to the handling of these two compounds. It may be of interest that in Venezuela, for example, over 300,000 human dwellings have already been sprayed with dieldrin for the control of the vectors of South American sleeping-sickness and malaria. This programme with dieldrin is continuing under the direction of the Malaria Division of the Ministry of Health and Social Welfare.—I am, etc.,

London, E.C.3 RUPERT SCOTT,
Chief Medical Officer,
The Shell Petroleum Company Ltd.

Idiopathic Pulmonary Haemosiderosis

SIR,—I was interested to read the article by Captain N. A. J. Hamer (*Journal*, April 23, p. 1008) particularly because another example of this condition has recently come to my notice.

A man, now aged 28, had a perforated duodenal ulcer closed at an emergency operation in 1952, and subsequently he has never had more than minimal dyspeptic symptoms; in particular he denies a haematemesis or melaena at any time. In October, 1953, he had pneumonia in Hong Kong and was away from work for five weeks; no details of this illness are available, although it is known that a chest film in January, 1954, was reported clear, but subsequently he noticed occasional blood in his sputum which he ignored because he felt in normal health. He was admitted to hospital on April 2, 1955, complaining of lassitude and a cough of three weeks' duration, which was productive of small amounts of blood-stained sputum. There had been no frank haemoptyses, but occasionally the sputum contained clots of blood: his appetite had been poor for several days, but his weight was steady.

On Examination.—A well-covered but remarkably pale man. T. 97.8° F. (36.55° C.); P. 118, regular; B.P. 150/70; heart normal. Abdomen: healed epigastric scar; no mass felt and no tenderness elicited. Chest: signs suggesting early consolidation at the left base.

R.B.C., 1.8 million per c.mm.; Hb, 36% (5.32 g.); colour index, 1.00; W.B.C., 11,900 (polymorphs 82%, lymphocytes 14%, monocytes 3%, basophils 1%, reticulocytes 4.2%); packed cell volume 15%. Blood group O; rhesus anti-D positive. Stool negative for occult blood (benzidine test). Direct van den Bergh negative. Serum bilirubin 0.7 mg.%.

A chest film on the day of admission revealed no definite abnormality, but a diagnosis of idiopathic pulmonary haemosiderosis was considered possible, and arrangements made for daily *x*-rays of the chest. On April 3 (the day following admission) there were multiple small, soft, round opacities scattered throughout both upper and middle lobes, with accentuation of the hilar shadows, but on April 4 the shadows were both smaller and harder in appearance, and on April 5 they had disappeared. On April 6 the medial parts of the left upper and middle zones and the right middle zone were granular in appearance; these appearances were unchanged on April 7, but they had become less marked on April 8, and the chest was radiologically normal on April 16.

Within 24 hours of admission the patient was running a temperature of 101° F. (38.3° C.), and in view of the persistent signs at the left base he was given a course of parenteral penicillin; moreover, his general condition was sufficiently poor for him to be given two pints (1.1 litres) of cross-matched blood on April 3. Following the transfusion his condition improved rapidly, and on April 6 a blood count showed: R.B.C. 3.02 million per c.mm., Hb, 52% (7.69 g.), reticulocytes 5.4%, M.C.H. 25.5 micromicrograms, M.C.H.C. 29.5%, M.C.V. 86 cubic microns. He was given tab. ferri. sulph. co., and on April 19 there were 3.69 million R.B.C. per c.mm., with Hb 73% (10.79 g.), and colour index 0.98. While in hospital he has continued to have small haemoptyses, but repeated examinations have failed to reveal tubercle bacilli or haemosiderin-containing macrophages in the sputum; neither have these cells been found in the gastric residue. There was no increase in the red cell fragility, and the platelets appeared normal in the blood examined.

This patient's illness is characteristic of the acute phase of early idiopathic pulmonary haemosiderosis, with the small haemoptyses, profound anaemia, and transient shadows in the chest films. It is not clear why haemosiderin-laden macrophages were not found in the sputum or gastric residue, but such a finding is not reported in every case in the literature. The course of the illness resembles that of a man aged 20[1] where the radiological opacities cleared rapidly after the first episode of haemoptyses with anaemia, but following a further attack there was "fixed" shadowing at the right base, the time interval between the first illness and the latter finding being practically three years. So far as the prognosis is concerned I would disagree with Captain Hamer's statement that the outlook is generally good in young adults when compared with children, in view of Walton and Williams's report[2] on the post-mortem findings in a youth of 19 with three years' symptoms.

I wish to thank both the medical officer-in-charge, R.N. Hospital, Plymouth, for access to the records and the Medical Director General of the Navy for permission to publish this letter. Surgeon-Commander P. H. K. Gray interpreted the chest films.—I am, etc.,

London. J. M. CLIFF.

REFERENCES
1 Cliff, J. M., *Brit. J. Radiol.*, 1953, **26**, 102.
2 Walton, M., and Williams, A. A., *British Medical Journal*, 1951, **2**, 390.

A New Barbiturate Antagonist

SIR,—We have recently treated four cases of barbiturate poisoning with the new barbiturate antagonist β methyl β ethyl glutarimide (N.P.13, "megimide"). The patients had taken between 36 and 90 gr. (2.4 and 6 g.) of barbiturate

several hours before admission. They did not respond to pain and all reflexes were absent on admission. Routine stomach washout was performed. With the first three patients, who had all taken approximately 36 gr. (2.4 g.) of barbiturate, 100 mg., 200 mg., and 250 mg. of N.P.13 respectively were given intravenously over the course of about one hour. At the end of this time the patients were groaning, making spontaneous movements of the limbs, and would respond to simple commands. After this they were easily rousable and their further course was uneventful. The fourth patient, a lady of 41 years, had taken 90 gr. (6 g.) of a barbiturate mixture, "tuinal," three hours before admission. A glucose drip was set up and 100 mg. of N.P.13 given into the drip every five minutes to a total of 600 mg. After ten minutes the corneal reflexes returned, and half an hour after the beginning of treatment the patient was talking and attempting to raise herself from the bed. Subsequently she was easily rousable, and two hours later was awake and would take food. Further progress was uneventful.

In these cases there was a significant rise in the level of consciousness during treatment with N.P.13, and in each case the improvement was maintained. In the first three cases only small quantities of the drug were available for treatment, and it is suggested that, as in the fourth case, larger amounts of N.P.13 should be used. No toxic or side-effects were noted with the amount of drug used. It is felt that N.P.13 offers considerable advantages over existing methods of treatment of barbiturate poisoning and merits further trial. We would like to thank Professor R. E. Tunbridge, Professor S. J. Hartfall, and Dr. O. H. J. Maxwell Telling, under whose care these patients were treated, and Nicholas Products Laboratories, Ltd., for supplies of N.P.13.—We are, etc.,

J. P. BINGLE.
J. G. WHITWAM.

Leeds, 1.

⁂ An article on the treatment of barbiturate poisoning with N.P.13 (and with D.A.P.T.) was published in last week's *Journal* (p. 1238).—ED., *B.M.J.*

Chronic Appendicitis

SIR,—I was most interested to read the article "Right Iliac Fossa Pain" (*Journal*, March 26, p. 752) and your leading article on "Chronic Appendicitis" (p. 776).

In 1953 in Capetown I investigated 200 consecutive cases of appendicitis, of which 93 were designated, clinically, chronic appendicitis.[1] These latter cases were admitted only after all investigations for other possible causes of their right iliac fossa pain had proved negative. The histological investigation, consisting of examination of serial sections, was undertaken by the pathology department of the University of Capetown. In this "chronic appendix" group only 19.4% (18 cases) showed appendicular histological abnormalities; 12.9% (12 cases) presented other intra-abdominal pathology. In the remaining 67.7% (63 cases) no pathological evidence could be found to account for the patients' pain. A follow-up questionary was sent to these 63 cases, but the response was too poor to allow of critical analysis.

These findings bear out the contention that the clinical and pathological correlation of chronic appendicitis is still far from satisfactory.—I am, etc.,

W. SILBER.

London, W.12.

REFERENCE

[1]Silber, W., *S. Afr. med. J.*, 1953, **27**, 187.

Aftermath of Hysterectomy

SIR,—I was writing of the new biochemical pathology of atherosclerosis and "the coronary woman"; Miss Louisa Martindale (*Journal*, May 7, p. 1155) is raking in the old sweet garden of memory and surmise. I would challenge any private or public clinic to produce even a ten-year attested follow-up in regard to blood pressures and the physical *cum* psychosomatic symptoms of patients treated by ovarian ablation, radium, or deep *x*-ray therapy for non-malignant conditions of the pelvis. Indeed, I would fling the gauntlet further and ask why it is that women suffer from acute lumbago (not disk disease) ten times less frequently than men do. It cannot be clothes or lack of exposure. Can it be an oestrogen *cum* adrenal protective mechanism? Tentative therapy of the male sufferer suggests that this is so.—I am, etc.,

V. B. GREEN-ARMYTAGE.

London, W.1.

Undergraduate Education in Preventive Health

SIR,—At the recent Royal Sanitary Institute Congress at Bournemouth (*Journal*, May 7, p. 1147) Professor R. H. Parry called attention to the need for closer integration of undergraduate medical training with the public health department. He also stated his belief that in time the general practitioner would be able to take over medical responsibilities at the health clinics. With this latter suggestion I am in full accord; but I submit that it cannot satisfactorily take place until Professor Parry's first proposal has been implemented and there has been a reorientation of undergraduate paediatric training. The work of the "baby" clinic is essentially preventive in outlook and deals with healthy babies. Undergraduate paediatric training, on the other hand, despite improvement in recent years, is largely concerned with disease. Anatomy and, what is more important, physiology, as taught to the medical student, are that of the adult. A course in paediatrics should begin with the study, largely on a practical basis, of the development of the child in its first two years and with the management of the healthy child in those years. Only when this has been achieved should the student go on to the study of departure from the normal. Here lies the way to that closer integration for which Professor Parry has asked.

It is useless to ask for earlier diagnosis of such conditions as cerebral palsy and congenital deafness when the newly qualified doctor is unacquainted with the normal development of locomotion and speech of the infant. Miss E. Whetnall (*Journal*, January 22, p. 227) has suggested the post-natal clinic as the ideal place for increasing the mother's awareness of the possibility and implications of partial deafness. All too often, however, the mother has to badger the doctor into such an awareness.

The syllabus and examination for the Diploma in Child Health lay much stress on the work of the school health service. The school medical officer should deliver a short series of undergraduate lectures and demonstrations on the handicaps of childhood and the application to them of the Education Act, 1944. The general practitioner may never see an example of the lipoidoses (I have not seen one in 11 years of clinical medicine). What he will have to deal with are the rheumatic child and the asthmatic child, not in isolation, but in relation to the world in which the child lives. These suggestions are, I submit, concrete examples of the application of such terms as preventive and social medicine to paediatrics.—I am, etc.,

A. YARROW.

London, N.12.

The Changing Face of Medicine

SIR,—Dr. Clifford Kennedy's article on "The Changing Face of Medicine" (*Journal*, April 30, p. 1045) was full of interest. I only want to refer to his courageous suggestion that merit awards for consultants should be done away with, and the money spent otherwise. I would suggest that the money be spent on a large increase in domiciliary consultations. Consultants and specialists are not synonymous terms, but specialists should be consultants. In the good old days a consultant was a wise doctor whom his colleagues liked to consult. The meritorious consultant got his reward in an increasing number of consultation fees. The same could easily be possible again if the administration permitted.

There would be many advantages. The waiting-lists for first visits to out-patients (though not necessarily for investigations) would be reduced. The consultant and specialist would be brought outside the hospital's four walls. The general practitioner would be brought into much closer contact with the leaders of the profession. It should be

remembered that every consultation provides the occasion for a miniature postgraduate course—which the hospital letter does not. If done on a large scale it would be necessary also to provide a small fee for the general practitioner, who has to find an hour of unpaid time at present. I would like to put this idea forward as a subject for discussion by the College of General Practitioners, and the Consultants and Specialists Committee.—I am, etc.,

Crowthorne, Berks. H. D. FORBES FRASER.

SIR,—This is not an attempt to discredit the National Health Service. On the contrary I would like to concede that the N.H.S. has proved a boon and a blessing to the public; but it would be too optimistic to expect that such a revolutionary measure would not reveal in practice imperfections and even faults. With good will and determination these could all be smoothed out.

From the young doctor's point of view the most pressing problem is the finding of suitable employment. Under present conditions unemployment is likely to increase as time goes on, unless a remedy is found. Paradoxically, the position is largely due to the fact that junior hospital posts have been greatly multiplied since the advent of the N.H.S. This has encouraged greater numbers of students to take up medicine than is necessary for the smooth maintenance of the service. After the completion of a year's hospital service there are not sufficient posts available to absorb all the young doctors looking for suitable and remunerative employment. The number of well-qualified registrars appears to be in excess of the number required to fill vacancies for specialists or consultants, and general practice is apparently not able to absorb all the young aspirants to general practice. We have on the one hand, therefore, the apprehensive or disappointed registrar, and on the other the young graduate with inadequate experience for general practice swelling the ranks of the unemployed. The remedy can, I believe, be found in a realistic redistribution of hospital beds, and reduction of the lists in the larger practices. The specialized hospitals are too big, and the G.P. hospitals too small and too few. General practice could also absorb more general practitioners, as there are still too many large practices employing assistants, where more principals are needed. The employment of an assistant in a large practice may be good business, but I refuse to believe that it is conducive to good medicine. Extension of the G.P. hospital to, say, 100 to 200 beds, where these could be fully utilized, would absorb many young graduates and afford the right kind of postgraduate training for the aspirant to general practice, and would save the more specialized hospital from being cluttered up with patients requiring no specialized investigation or treatment. The patient would also gain by remaining, while in hospital, under the care of the home doctor. The G.P.'s status would be enhanced. He would be able to take a practical share in the main divisions of medical work, medicine, surgery, anaesthetics, and midwifery, while co-operating with the consultant or specialist where necessary. With ready access to the regional laboratory he could conduct most of his own investigations.

I consider I have been very fortunate in always having been on the staff of local hospitals, general and maternity, and child welfare clinics. With the facilities provided by the regional laboratories I do the major part of the medical investigations of my practice, have conducted something like 4,000 maternity cases with only two maternal deaths, have given thousands of general anaesthetics, including spinal, and from time to time have been doing straightforward surgery without a single mishap. I have therefore been fortunate enough to be able to avoid becoming a signboard. While not earning the remuneration of the doctor with the big list, I have experienced a full and satisfactory professional life.

Under present conditions the G.P. has not the facilities to give the best of which he is capable. The specialist's time to a considerable extent is wasted with cases which could be looked after by the family doctor. Under the conditions I have visualized there would be a better all-round use of medical personnel and of hospital beds, and I believe a reduction in hospital expenditure, while the training provided for the young aspirant, whether for G.P. or specialist post, would be more in keeping with his or her respective needs and requirements.—I am, etc.,

Fraserburgh. J. MACLEOD.

Opportunities for Medical Practice

SIR,—Sir Stanley Davidson's article (*Journal*, May 14, p. 1171) makes clear the urgent need for a change in the official attitude to medical education and to medical practice. It is obvious that medical practice, in the sense that this is now understood, cannot continue to absorb the numbers of practitioners now becoming qualified. From now on, either the number of doctors must be kept constant, or the remuneration *per capita* must fall, or the State health services must pay out more and more. Is there, in fact, any over-doctoring in the absolute sense? A more liberal supply of doctors, if this implies increased medical care and the disappearance of the "overworked practitioner," might be a very good thing indeed. And surely medical practice is but one aspect of the aim of medical education. The modern world needs medical men in many fields—in commerce, law, scientific research, and even politics. My guess is that demand for medical graduates in these fields will increase steadily. The men working outside medical practice are not a loss to the profession. They are vital to it, fully utilizing a general medical education, and continuing throughout their careers to maintain contact with practising doctors.

It would be dangerous in the extreme to tamper with the autonomy of universities in the admission of students for medical training, on the basis of the alleged over-doctoring of the population. A plea may be made, however, for cutting out some of the detail in the present medical course, which is designed to suit the traditional needs of general practitioners, some of which needs hardly exist any longer. General practice has rapidly become a specialty where, in the future, standards should be established and guarded by the College of General Practitioners. The undergraduates' course could therefore be redesigned with an eye to producing a new type of medical graduate much better fitted to choose between practice and the ancillary branches of medicine. The course could be shortened from the present six years to five years, or even less, and made more intensive in its purely scientific and clinical aspects. Undergraduate "specials," which are cram courses designed to suit the needs of a general practitioner of 30 or more years ago, could be covered more generally in medical or surgical teaching. The present state of affairs is uneconomic and threatens to become more so. If things continue as they are a medical man will have spent one-half his life as a liability on his parents or on the the State, only to find that in the second half he is barely able to meet his economic responsibilities.—I am, etc.,

Stourbridge. O. C. FORBES.

Cancer of the Upper Alimentary Tract

SIR,—Dr. L. D. Sanghvi and his colleagues (*Journal*, May 7, p. 1111) point out that intra-oral carcinoma accounts for 35.9% of all cancer cases in Bombay, whereas only 6.7% of cancers treated in London hospitals were situated in the oropharynx. These striking figures indicate that interest must presumably focus on some outstanding difference between the habits of Indians and Europeans.

Smoking and chewing tobacco (the practices investigated in the article by Dr. Sanghvi *et al.*) have, after all, got their western equivalents. No European, however, constantly subjects his oral cavity to the intense (but delicious) irritation of a curry, while most Indians do so twice daily. As one who has experienced the prolonged intra-oral burning which invariably follows an Indian curry, I am surprised to find that

the writers did not ask their patients for data concerning the spices in their diet. Surely this factor cannot be omitted when investigating the aetiology of carcinomas of the mouth and pharynx in Indians.—I am, etc.,

London, E.1. F. E. LOEFFLER.

Giant Cells in Measles

SIR,—I read with interest the annotation on "Giant Cells in Measles" (*Journal*, April 30, p. 1078). Three years ago I performed a necropsy on a child dying of measles who had been treated with antibiotics and showed apparently pure measles pneumonia. I do not remember seeing giant cells within the bronchi, but these were very frequent within the alveoli and showed degenerative appearances. They appeared to be formed by desquamation and fusion of alveolar epithelium. Small rounded acidophil intracytoplasmic inclusion bodies were very frequent within them and also within single epithelial cells. No giant cells could be found in the pulmonary lymph nodes, however. It would certainly seem very reasonable that these cells, quite possibly containing inclusions, should be found in the sputum.—I am, etc.,

Southampton. R. A. GOODBODY.

Chicken-pox Quarantine

SIR,—Dr. J. J. Linehan's scepticism as to the protective value of chicken-pox against zoster (*Journal*, May 7, p. 1156) will no doubt endure until it is possible to grow the relevant virus and then submit suitable volunteers to challenge with it. Otherwise the available evidence must be based on histories that are rarely verifiable and on one's own personal experience. On this point, for some years past I have made it a practice to question—and examine—all cases of zoster for evidence of previous chicken-pox. So far I cannot recall one that convinced me. This may of course be no more than coincidence, though I wonder. In any event, Dr. Linehan will, I am sure, agree with me that to rely on histories in infectious work is to court, and not infrequently to experience, disaster.

Common ground at present is that the one disease may give rise to the other, and that, so far as virology can ascertain to-day, the two viruses appear to be identical. The hypothesis that "herpes zoster is a response of an immune person to an overwhelming dose of varicella-zoster virus" is surely dismissed by those cases of zoster (I have seen two recently) who proceed to develop a generalized chicken-pox eruption. Here it seems that a hitherto localized infection suddenly spills over into the blood. Incidentally, I have never known the converse to occur. It might be argued with more cogency that a localized infection like zoster will not give rise to such a stable immunity as when the virus has challenged the whole body as in chicken-pox. Perhaps I may here be allowed to cite a personal experience. Having enjoyed a mild attack of shingles at school, I have subsequently been exposed to chicken-pox on literally thousands of occasions, but I have never developed the disease. Clearly, in some cases at least, zoster can protect against chicken-pox as well.—I am, etc.,

Isleworth. G. E. BREEN.

Salk Vaccine

SIR,—Dr. J. G. Humble (*Journal*, May 7, p. 1154) asks if rhesus sensitization is a possibility after inoculation with anti-poliomyelitis vaccine. At the suggestion of Professor Stuart Harris, samples of the vaccine prepared in this country have been studied at this centre. A number of *in vitro* inhibition tests against rhesus anti-sera (anti-D, anti-C, anti-E, and anti-c) have been carried out, but so far I have not found that the material contains any substance capable of inhibiting either immune rhesus antibodies or the normal isoagglutinins. As yet there has been no opportunity of estimating whether the vaccine is more powerful *in vivo*.—I am, etc.,

Sheffield, 10. J. S. CAMPBELL.

Ban on Heroin

SIR,—Mr. D. K. Mulvany's letter on the subject of the ban on heroin (*Journal*, May 14, p. 1221) contains the extraordinary suggestion that a consultant should have to add his signature to the general practitioner's prescription so that "the procuration of heroin could be tightened up." Apart from the difficulty of obtaining his signature for each prescription in the case of a patient dying at home, has Mr. Mulvany considered the implications of his suggestion? One of these appears to be that general practitioners' lax prescribing of heroin is a source of danger. The other is that consultants are more responsible than general practitioners in prescribing dangerous drugs.—I am, etc.,

Farnham Common. DAVID MILWARD.

SIR,—I cannot believe that the individuals who have been responsible for the decision to ban heroin fully appreciate its indispensable role in the relief of suffering and pain associated with incurable malignant disease. It is also irritating to have handed out to us the misinformed statement, which surely does not find support in the experience of unbiased medical men, that we already have efficient substitutes for heroin. What a boost this is for the drug houses, but what a piece of presumptuous poppycock. With growing numbers of incurable cancer patients coming under our care, the ban can only be regarded as an iniquitous action which we can scarcely condone.

Apart from the few troubled voices of those crying in the wilderness, I am not aware of an organized protest from any of the official bodies within the profession. Is there any reason why we cannot have a nation-wide ballot—conducted, for example, by the B.M.A., the Royal Colleges, or the College of General Practitioners—in order to determine the consensus of medical opinion in the matter? The results could form the basis of a concerted protest by the profession to the Government against removal from our pharmacopoeia of this valuable and irreplaceable drug. The banning of heroin, in its practical consequences and in the manner in which it has been decreed, poses an issue of considerable moment to all who practise the healing art.—I am, etc.,

Perth. R. G. SIMPSON.

SIR,—May I be allowed to add my protest in support of Dr. A. H. Douthwaite (*Journal*, April 9, p. 907), Dr. R. Hale-White (*Journal*, April 30, p. 1092), and others on the ban on heroin? As an anaesthetist I seldom have recourse to this drug, but there are occasions when it is the only effective remedy. Cannot the B.M.A. take a really strong and conclusive line on this question?—I am, etc.,

Hove. J. H. CRAWFORD.

Food-poisoning

SIR,—May I draw attention to a small error in Dr. Christopher Hardwick's interesting article (*Journal*, May 14, p. 1205)? Unless corrected this may give rise to some confusion. It is quite correct to say that *Amanita phalloides* may be eaten in mistake for the field mushroom. Indeed, this fungus is said to be responsible for 90% of the deaths due to mushroom poisoning. However, the English name for this variety is not "fly agaric," as Dr. Hardwick states, but "death cap."

The fly agaric is the *Amanita muscaria* and contains muscarufin as well as muscarine, and this presumably accounts for its distinctive colour. It is the decorative fungus which may be seen ornamenting the pages of many fairy-tale books or the back-cloth of the pantomime. Its former use as a fly killer has determined its name in many languages besides Latin and English. The Russian "mukhomor" means "fly-death." The fly agaric has a scarlet cap with white spots and because of this brilliant colouring is very unlikely to be eaten in mistake for some other variety.

The death cap on the other hand is white, almost entirely lacking in pigment. It may grow on grassland verging woods. It can be distinguished from the field mushroom (*Psalliota campestris*) by the colour of the gills, which are white, not pink, brown, or black, and by the volva, which is a distinct cup at the base of the stem presenting (hence the botanical name) a phallic appearance in the young specimen.—I am, etc.,

London, S.W.17. BRIAN H. KIRMAN.

Difficulties of Child Adoption

SIR,—Our attention has been drawn to Dr. P. M. Fea's letter (*Journal*, April 30, p. 1096). I am afraid the fact is that there simply are not any girls of about 5 available for adoption by anybody. Girls are far more in demand than boys, and every society has a long waiting-list of adopters waiting for girl babies. This is aggravated by the fact that girls are also more readily received by grandmothers, and even by employers, than boys, so that not only are more girls than boys asked for, but fewer girls than boys are offered for adoption. Only about 1% of the "inmates of homes" are available for adoption, and it is safe to say that none of those available is a girl of 5—girls have all been adopted long before reaching that age. Once a child reaches school age unadopted, the chances of its being offered for adoption are much less than before, since a mother who has managed to keep her child with her up to that age finds her task much easier once the child goes to school. And a girl of 5 who is orphaned usually has relatives who are able and willing to take her on. Every adoption society is overwhelmed by requests for toddler girls, which it would be happy to satisfy if the children were available—we should not be concerning ourselves with adoption at all if we preferred to leave children languishing in homes. But the number of people wanting to adopt children as a whole is about 10 times the number of children offered for adoption, and in the case of girls probably 20 times. For girls of 5 it must be hundreds to one.—I am, etc.,

London, N.W.11. M. E. EDWARDS,
Chairman, Standing Conference of Societies Registered for Adoption.

British Society of Dental Hypnotists

SIR,—At the annual general meeting of the British Society of Dental Hypnotists it was decided unanimously to change the name of the Society to the Dental and Medical Society for the Study of Hypnosis. This was done at the request of the increasing number of medical practitioners who have joined the Society and taken theoretical and practical study courses in the use of hypnosis. They felt that it would be a wise thing if the Society were expanded into dental and medical sections, with separate committees and a joint committee to dictate general policy. Some of our future meetings will be of a general nature and others of more specialized type to suit each profession. The courses of instruction will continue but will become, in their later stages, more specialized in character, and the students will separate for this purpose. The Society now numbers nearly 200 members, of whom over 150 have attended the courses of instruction we have held on the theory and practice of hypnosis, its uses, limitations, and dangers.

The Society, since its inception, has laid special emphasis on the needs of the general practitioner both of medicine and dentistry, and in view of the recent B.M.A. report supporting further teaching and investigation in hypnosis we should welcome further members of both professions who are interested. At our annual general meeting held on May 3 the following resolution was passed unanimously: "This Society feels strongly that the use of hypnosis should be confined to the members of the medical and dental professions."—I am, etc.,

London, W.1. E. E. WOOKEY,
Chairman.

Obituary

W. M. ROBSON, M.D., F.R.C.P.

Dr. W. M. Robson, consulting physician to Northampton General Hospital and to the Oxford Regional Hospital Board, died at his home at Northampton on May 10. He was 77 years of age.

William Morton Robson was born in 1877, the son of John S. Robson, J.P., of Butterknowle, Co. Durham, and was educated at St. James's School, Bishop Auckland, and at the Forest School, Walthamstow. He entered Guy's Hospital as a medical student in 1895 and qualified M.R.C.S., L.R.C.P. in 1901, taking the London M.B. in the same year. After holding several hospital appointments at Guy's and other London hospitals, he went to Northampton in 1903 as junior medical officer at St. Andrew's Hospital, an appointment which gave him time to work for higher qualifications. He proceeded to the M.D. in 1903, winning a gold medal, and obtained the M.R.C.P. two years later, when he was elected to the honorary staff of Northampton General Hospital as assistant physician with charge of the electrical department. This was the forerunner of the present *x*-ray department. In due course Robson became radiologist as well as physician, and it was in no small part due to his influence that an anonymous benefactor subsequently gave much of the present equipment of the *x*-ray department to the hospital. Robson's skill as a clinician helped him greatly in his radiological duties, and for many years he was in charge of the diagnostic and radiotherapeutic work. His diagnostic reports, notable for their brevity, were always written by his own hand; in *x*-ray therapy he followed closely the technique of Coutard, and, though his dosage by modern standards was often low, his results were remarkably good and he seldom distressed patients by his treatment. His interest also extended to venereology, and he established the venereal diseases clinic, which remained under his direction until his final retirement in 1950. During the first world war he served with the rank of major in the R.A.M.C., and was attached to Berry Wood Mental Hospital, which had been taken over for the reception of Service casualties.

Robson was elected F.R.C.P. in 1920, and for thirty years as senior physician was a central figure in the life of the Northampton General Hospital. Always quietly courteous and thoughtful, his judgment was extremely sound and his opinion carried weight not only in clinical matters but also in the board of management on which he served many years. He was honorary secretary of the old Northamptonshire Division of the British Medical Association from 1922 to 1927; chairman of the Division in 1930–1; and honorary secretary of the Northamptonshire Branch in 1935. He wrote little, but, despite many hospital commitments and a considerable private consulting practice, he found time for relaxation in sport and the entertainment of his friends. He was an excellent shot and in later years a keen and expert fisherman. A genial host—and a connoisseur of port—he was a master of the bridge table. He leaves a widow and one daughter.—R. O. L.

W. F. ANNAND, M.D.

The medical profession in Coventry heard with deep regret of the death on May 6 at the age of 75 of Dr. W. F. Annand, consulting physician to the Coventry and Warwickshire Hospital.

William Fraser Annand was born at Peterhead, Aberdeenshire, on September 20, 1879, and went to school at South Shields, where his father, R. C. Annand, J.P., was an engineer and an inventor of printing machines. He began his medical studies at Durham University and went on to University College Hospital, London, where he had a distinguished student career, gaining gold medals in medicine, surgery, and pathology. He graduated M.B., B.S. at London University in 1903 and proceeded to the M.D. two years later. After holding house appointments at University College Hospital, the East London Hospital for Children, and at Queen Charlotte's Hospital he went into general practice at Stafford, where he was appointed honorary physician to the Staffordshire General Infirmary.

In 1909 Annand moved to Coventry, and three years later began his long association with the Coventry and Warwickshire Hospital as honorary anaesthetist. In 1919 he became honorary physician to the hospital, taking a very keen interest in its development and serving on the board of governors. For a long period he was chairman of the medical advisory committee. On his retirement in 1939 the board of governors appointed him honorary consulting physician to the hospital. He was chairman of the Coventry Division of the British Medical Association in 1925–6.

The death of Dr. Annand's wife in 1939 was a great blow to him, for her gaiety and zest of life were a constant joy to him after hours of heavy responsibility. During the second world war he returned to active duties at the Coventry and Warwickshire Hospital, and in 1941 he received Royal commendation for his work during the air raids. He finally retired in 1946, but four months later, while on holiday, he had a severe heart attack and since then had had to lead the life of an invalid. His recreations were golf and bridge, and fortunately he was able to continue to play bridge up to a week or two before his death. He is survived by a son and a daughter, who is matron of the National Temperance Hospital, London, and to them and to all his relatives we extend our deepest sympathy. In the passing of William Fraser Annand, Coventry has lost a great physician and his colleagues a loyal and trusted friend.—W. P. E.

T. W. J. JOHNSON, M.D., F.R.C.P., F.R.A.C.P.

Dr. T. W. J. Johnson, consulting physician to the Auckland Hospital, New Zealand, died at his home at Auckland on October 16, 1954, after a short illness.

Born at Auckland in 1885, Thomas William James Johnson was educated at Thames High School and at Auckland Grammar School, where he won a junior scholarship to Otago University. At the university he more than maintained his early promise and gained many prizes, including the first award of the medical travelling scholarship. He graduated M.B., Ch.B. at the University of New Zealand in 1909, and then held posts at Dunedin Hospital before coming to London, where he worked at the Middlesex Hospital and the Maida Vale Hospital for Nervous Diseases. After obtaining the London Conjoint diploma in 1911 and the M.R.C.P. in the same year, he returned to New Zealand, where he proceeded to the M.D. in 1912 with a thesis on the apex beat. For the next 10 years he was in practice at Napier, being elected to the honorary staff of the local hospital.

In 1921 Johnson again came to London for postgraduate studies, after which he settled at Auckland, where in due course he was appointed senior honorary physician to the Auckland Hospital, a post he continued to hold until his retirement in 1951. He was elected a Fellow of the Royal College of Physicians of London in 1932. Six years later he became a Foundation Fellow, a Censor, and a member of the Dominion Committee of the Royal Australasian College of Physicians, and in 1942 he was elected a vice-president of the College. He was an examiner in medicine for the University of New Zealand, consulting physician to the Royal New Zealand Navy and to the Fiji Government in New Zealand, and had served on the Medical Council of New Zealand. He also did good work as the chairman of the Miners' Pension Appeal Board and of the Dominion Tuberculosis Committee, and he helped to establish the Auckland Clinical Society and to found the medical library at the Auckland Hospital. When he retired in 1951 he was appointed consulting physician to the Auckland Hospital and became a member of its committee on appointments. From 1936 to 1938 he was chairman of the Auckland Division of the British Medical Association. Johnson was an excellent teacher. He expressed himself clearly and in simple language and gave every possible assistance to his students. To the newly qualified he was a never-failing source of encouragement. He helped them in their work when the need arose, and his advice, eagerly sought, was of great value to them in their careers. An all-round sportsman, he played hockey for his university, and in later life became an expert angler and a competent golfer. A man of many hobbies, he was particularly interested in the history, folk-lore, and language of the Maori people, and was well versed in the natural history of New Zealand. He is survived by a widow and two sons, both members of the medical profession.

OTTO ROSENHEIM, Ph.D., F.R.S.

Dr. Otto Rosenheim, who made notable contributions to biochemistry and physiology, died in London on May 7 at the age of 84.

Otto Rosenheim was born and educated in Germany. At the University of Würzburg, where he took his Ph.D. degree, he worked under Emil Fischer, and later he continued his studies at the Universities of Bonn and Geneva. In 1895 he came to England, where he secured an appointment at the University of Manchester. Six years later he moved to London, having obtained a research studentship in pharmacological chemistry at King's College. In 1904 he was appointed lecturer at King's College and, later, assistant professor of physiology. He also held a readership in biochemistry in the University of London until 1920. Having given up his official appointments, Rosenheim became a voluntary worker at the National Institute for Medical Research at Hampstead, where his research into the chemistry of sterols with Dr. Harold King led to some notable advances. Rosenheim was elected a Fellow of the Royal Society in 1917 for his work on brain chemistry. He married Miss Mary Christine Tebb, whom he met when she was on the staff of King's College, and with whom he collaborated in research work. She died in 1953.

We are indebted to Dr. HAROLD KING for the following appreciation :

It is difficult in a few words to do justice to the work of a born investigator like Otto Rosenheim. He chose for his field of operations physiological chemistry, and at King's College, London, between the years 1901 and 1920

contributed fundamental observations to this subject. With Tunnicliffe he was concerned with the toxicity of beer containing selenium which arose from the sulphuric acid used in preparing the sugars for fermentation; and in another inquiry he showed that formaldehyde—1:5,000 in milk and 1:9,000 in food—had no effect on healthy children. With Locke, Rosenheim took part in a classical investigation: they devised a new perfusion method for the mammalian heart, using dextrose in oxygenated Ringer solution, and followed the sugar metabolism. An outstanding piece of research work then followed in which Rosenheim was assisted by Mary Christine Tebb, who later became his wife. They took up the chemistry of brain, and incidentally laid low the myth of protagon as a single entity, but, more important, they devised methods for the separation of the constituents of the brain—phrenosin, kerasin, and sphingomyelin—leading to the elucidation of the structure of the two former substances. At King's College, too, Rosenheim demonstrated that, contrary to Dixon and Taylor's findings, an extract of placenta had no pressor effect if there was no putrefaction.

After five years of retirement, Rosenheim joined the National Institute of Medical Research at Hampstead as a voluntary worker and revelled in the facilities provided. With Dudley he cleared up the distribution of two mammalian bases of unknown function, spermine and spermidine, and elucidated their structures. A fruitful co-operation with Webster resulted in the proof that the substance which on irradiation cured rickets in rats, the so-called provitamin-D, was ergosterol. Much has flowed therefrom. In association with Drummond he delved in the vitamin-A field and found that arsenic trichloride gave with cod-liver oil a blue colour proportional in intensity to the vitamin-A content. Other fish and bird oils were examined, some of which are now in daily use in medicine. The writer was fortunate in a collaborative effort with Rosenheim whereby revolutionary formulae were proposed for the sterols and bile acids in 1932. These have received universal acceptance and have led to remarkable advances in the knowledge of certain heart poisons, sex hormones, and principles of the adrenals.

The death of Dr. J. MACK. JOHNSTONE occurred at his home at Leven, Fife, on April 17. James MacKersie Johnstone was born at Muirkirk, Ayrshire, on August 20, 1881, but most of his early life was spent in Lanarkshire. He received his medical education at Edinburgh University, where he graduated M.B., Ch.B. in 1902. After a few months as a locumtenent he went as assistant to Dr. W. Young, of West Calder, Midlothian, and then took up practice in 1905 in the Lanarkshire village of Tarbrax. After service in the first world war he returned to his practice, but in 1919 he moved to Leven, where he continued to practise until his death. Dr. Johnstone was a keen member of the British Medical Association, and from 1924 to 1947 he carried out the duties of honorary secretary of the Fife Branch, as well as those of honorary secretary of the Fife panel committee. In 1947 his colleagues showed their appreciation of his devoted services by making a presentation at a dinner given in his honour, and later they elected him president of the Fife Branch for 1948–9. He also served the profession on the Scottish Committee of the B.M.A. for many years, was vice-chairman of the Fife executive council, and a member of the East Fife hospitals management board. Although he had not enjoyed the best of health for some time, his sudden death came as a great shock to his colleagues. Our sympathy goes out to his widow, daughter, and two sons.—A. M. G.

Mr. A. H. B. HEESOM, dental surgeon to the East Surrey and Redhill County Hospitals, died at his home at Reigate on April 19 at the age of 54. Alan Hedley Beecroft Heesom was born at Redhill on September 29, 1900, and was educated at Marlborough and at Guy's Hospital, qualifying L.D.S. in 1926 and taking the Conjoint diploma of M.R.C.S., L.R.C.P. in the following year. After holding the appointment of dental house-surgeon at Guy's Hospital he joined his father, Mr. E. E. D. Heesom, in 1929, succeeding to the practice two years later, when his father retired. He was honorary dental surgeon to the East Surrey Hospital from 1934 until the inception of the National Health Service in 1948, when he was appointed senior hospital dental officer to the Redhill Group of Hospitals. He was extremely popular with all his patients and his professional colleagues, both medical and dental, as was shown by the very large attendance at his funeral service, the congregation being representative of all walks of life in the borough. He is survived by his widow and a son and a daughter.

The death occurred at Bolton on April 22 of Dr. JAMES SCOTT, honorary consultant gynaecologist to the Bolton Royal Infirmary. He was 73 years of age. James Scott was born on February 26, 1882, and received his medical training at Edinburgh University, where he graduated M.B., Ch.B. in 1907. He went to the Bolton Royal Infirmary as a house-surgeon in the same year, and remained for three years. During this time his ability and keenness were fully appreciated, with the result that he went as assistant to one of the staff who was also in general practice. In 1911 he was appointed to the staff of the Bolton Royal Infirmary as honorary assistant surgeon, and in 1913 he obtained his own general practice at Bolton. With the outbreak of the first world war in 1914 he joined the R.A.M.C., retiring with the rank of captain, and during his service he was awarded the Military Cross. He returned to the staff of the Bolton Royal Infirmary in 1920, and from then on his main interest was in gynaecology. In 1929 he was appointed honorary gynaecologist to the Royal Infirmary, where he founded the department. He remained in this position until 1948, when he retired from the active staff and was appointed honorary consultant gynaecologist. Dr. Scott was hard-working, conscientious, and took scrupulous care in all he did. He was a very capable surgeon, and was always insistent that everything in the operating theatre should be exactly as he wished it, but he was completely disinterested in the clock. He was never happier in the theatre than when doing a colporrhaphy, which provided him with plenty of opportunity to show his care and neatness. He continued in general practice until 1954, when he was forced by ill health to retire, and later in the year he returned to his beloved Scotland, living at Selkirk.—T. N. H.

Dr. LLEWELYN WYNNE DAVIES, who was formerly assistant director of medical services in Nigeria, died on April 24, aged 80. The fourth son of the Reverend David Davies, of Llansilin, Llewelyn Wynne Davies went to school in Oswestry, and studied medicine at King's College, London, and Edinburgh University, where he graduated M.B., Ch.B. in 1897, proceeding to the M.D. in 1903. After holding resident appointments at a number of hospitals, including The Hospital for Sick Children, Great Ormond Street, he continued his postgraduate studies at Heidelberg and Berlin. He also travelled widely as a ship surgeon and was in Japanese waters during the Russo-Japanese War. For some years thereafter he was a general practitioner in Hayle, Cornwall, and then joined the Colonial Medical Service in 1911, being sent to Nigeria, where he did pioneer medical work in unexplored areas of the country. During the first world war he saw active service in German-East Africa, Mesopotamia, India, and Afghanistan, being mentioned in dispatches. He was appointed O.B.E. in 1919. Retiring from the Colonial Medical Service in 1931, he farmed for some years in Llansilin and took an interest in many aspects of country life. Few men were so capable of offering intelligent advice on varied subjects. A keen antiquarian, he was president of the Offa Field Club and a committee member of the Cambrian Archaeological Association. He was also well known as a churchman, being a member of the governing body of the Church of Wales. A justice of the peace, he served on many committees concerned with local government and with the University of Wales. Throughout his life he maintained a fatherly interest in

Llansilin, and his home there was the centre of village life. Although unmarried, he loved family life and was always interested in child care. By young people in particular a visit to his home was never to be forgotten. Two of his nieces are medical practitioners.—I. H.

The death occurred suddenly at Oxford on May 9 of Dr. C. A. R. MCCAY, who had been in general practice there for more than 30 years. Charles Alexander Ramsay McCay was born at Castlederg, Co. Tyrone, on May 12, 1890, the son of the late Rev. James McCay, and received his medical training at the Meath Hospital. He took the Irish Conjoint diploma in 1916, and then immediately volunteered for service with the R.A.M.C. in the first world war, attaining the rank of captain. After three years' service in France he returned to Dublin, where he took the D.P.H. at the Royal Colleges in 1919, and the F.R.C.S.I. (in the following year), gaining first place in the latter examinations. He then held resident posts in Dublin and Northampton before settling at Oxford in 1922, in partnership with Dr. Robert Hitchings. He became the senior partner in 1930, when Dr. Hitchings retired, and remained so until the time of his death. He was deeply interested in medical activities of all kinds, and his influence was widely felt. He was a product of the old school, and firmly believed that the doctor should also be the friend and counsellor of his patient. He set himself and his colleagues a very high standard in all medical matters, and strongly opposed any tendency to undermine the responsibility and position of the general practitioner. He was a man of fine character—generous and warm-hearted—and by his passing Oxford has lost a really good doctor, and many people a trusted friend and adviser. He is survived by his widow, three daughters, and two sons.—J. C. S.

Sir ROBERT MCCARRISON writes: As one who enjoyed the friendship of that grand family doctor, Charles McCay, may I quote these lines which so fittingly tell what manner of man he was:

"But once I pass this way
And then—no more.
. . . . . .
So while I may,
With all my might,
I will essay
Sweet comfort and delight
To all I meet upon the pilgrim's way."

This might well be his epitaph; for he will long be held in affectionate remembrance by the many to whom, in his pilgrimage, he brought comfort and healing both as friend and as doctor.

The obituary of Mr. R. DAVIES-COLLEY was printed in the *Journal* of April 30 (p. 1097). A. E. S. writes: When "D.C." as he was always known, returned from the first world war he arrived at Guy's arrayed in a grey morning-coat and top-hat. Later, I think, he got a little less formal, but usually wore grey. He was very polite and addressed all nurses (to their gratification and astonishment) as sister. As Mr. T. B. Layton writes, he never showed any emotion. Everybody knew that he had been keen on obstetrics. He was a good surgeon, but had not the tidy and precise habits of Mr. Fagge, whose house-surgeon I was when D.-C. was assistant surgeon. A popular, bland, and imposing figure, Davies-Colley will be remembered with affection by all who came under his influence.

Medico-Legal

PSITTACOSIS IN FAMILY

Judgment was entered for defendants with costs by Mr. Justice Gorman in the High Court on May 13 in the action for damages brought by a family of five who alleged they contracted psittacosis from a parrot bought at a pet shop. The defendants were the Regent Pet Stores (Palmers) Ltd., of London, N.W., who denied that any parrot they had sold was suffering from psittacosis or that there was any breach of warranty or negligence by them in connexion with the sale of the bird. The plaintiffs were Mr. W. C. Downes, a trolleybus driver, Mrs. F. A. Downes, his wife, G. W. Downes, now aged 14, Mrs. Daphne Chalk, aged 21, and Elaine Downes, aged 9, all of London, N. Entering judgment for the defendants, his lordship ordered Mr. Downes, who was legally aided, to pay £36 towards the costs. Giving judgment, his lordship said he was satisfied that, while Mr. W. C. Downes, the father, suffered from psittacosis, and it was probable that the boy Graham, Mrs. Chalk, and the girl Elaine had too, he was not satisfied that Mrs. Downes had. The allegation of breach of warranty was that the parrot was weak, dejected, and suffering from psittacosis when it was sold on December 18, 1952, and subsequently died on December 29, 1952. He could not accept this, and preferred the evidence of the defence witnesses that the bird was in good condition when it left the pet stores. It had been stated that the birds in the pet stores were inspected frequently every day, and there had been no indication that this particular parrot was out of condition. In any case, added his lordship, there was a room set aside as a hospital for sick birds. The greatest possible care was given to birds and pets, and there was no evidence whatever that there had been any sort of trouble of any description in respect of pets and their care. He was quite unable to say on the evidence that the bird was suffering from psittacosis at the time of the sale.

FAULTY McGILL TUBE CAUSES DEATH

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

On March 1, 1955, Karen Jennifer Wills, aged 3 years 11 months, was admitted to the Southern Hospital, Dartford, for operation to correct a slight squint of the left eye. Her general health was good, and the operation was performed next day.

Premedication for the anaesthetic consisted of "nembutal" 1½ gr. (100 mg.) and atropine 1/100 gr. (0.65 mg.), followed by ether anaesthesia. After induction and intubation at 10.40 a.m. the operation began at 10.52. Oxygen was slightly increased because of some coughing on the tube similar to hiccups, and the anaesthetist passed his finger into the child's mouth to ascertain that things were all right. Later she became slightly cyanosed, so that the oxygen was again adjusted and a further check with the finger in her mouth was carried out. Her colour was then restored. Five minutes later the operation was concluded. She was then cyanosed and little or no chest movement could be seen. Resuscitative measures were at once applied and maintained for twenty-five minutes, but without avail. Only then was the tube taken out of the child's mouth, and it was found to have a transverse fracture about 1½ in. (4 cm.) from the end nearest the lips, behind the teeth at the back of the tongue.

How this break occurred, and precisely what caused the lack of oxygen contributing to the vagal inhibition which caused her sudden death, did not become clear from the evidence at the inquest held by the coroner for North-west Kent at Dartford on March 8 and 29.

The tube used was a nasal tube, deliberately selected. It was examined by the anaesthetist, who saw no sign of fracture, and no force was used in removing it. A representative of the suppliers said that although tubes had been known to split longitudinally he had never known of a split round the tube. The minimum pull required to break a similar tube on test was 28 lb. (12½ kg.). Although autoclaving tended to harden tubes, this one did not appear to be hard.

Mr. W. H. Stevens, an expert on rubber and plastics, examined the broken tube, which in his view could have broken as it had only by force exerted along its axis. He found that it had perished to some extent, because when he

squeezed it longitudinally cracking was produced, and the cracks contained foreign particles of, he thought, a siliceous character. One crack contained reddish rust. He was unable to break the tube in the way it had broken except by pulling hard along its axis. He did not think that the degree of perishing which he found could have been seen with the naked eye.

A verdict was recorded of death by misadventure from vagal inhibition.

£2,000 DAMAGES FOR RHEUMATOID ARTHRITIS

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

From August, 1950, to April, 1953, Mrs. Maureen McKendrick, a teacher at St. Conval's Junior Secondary School, Glasgow, had as her class-room what had been the back kitchen in the house which formed the school annexe. It was a badly heated and ventilated room, the temperature of which was usually about 50° to 52° F. (10°–11° C.), but as low as 42° F. (6° C.) in winter. It never rose to the 56° F. (13° C.) required by the school regulations. In winter Mrs. McKendrick and her class wore their overcoats in an effort to keep warm, and when conditions were unendurable special arrangements were made for the class to be transferred to the main school building. During this period Mrs. McKendrick's health gradually deteriorated, until she became crippled by rheumatoid arthritis.

Mrs. McKendrick brought an action against her employers, the Glasgow Corporation, alleging that by reason of the conditions in which she was required to work the corporation had failed to take reasonable care for her safety, as a result of which her rheumatoid arthritis had been brought about. The corporation denied that the room was in an unhealthy or dangerous condition, and said that it had had to be used at the time because of shortage of teaching accommodation. Its use had since been discontinued because it was not satisfactory from a teaching point of view.

In the Court of Session evidence was led on behalf of the corporation that damp and cold were not the cause of rheumatoid arthritis. Dr. Dudley Hart, of Harley Street, agreed in cross-examination that for a slim young girl in her twenties conditions of cold and damp in a room in which she had to work would be unsatisfactory, but said that from the point of view of causing rheumatoid arthritis cold and damp had no relevance. Dr. J. P. Currie, of the Glasgow Infirmary, a member of the Empire Rheumatism Council, said that although cold and damp were normally associated with rheumatism in general that was in his opinion a fallacy. Although it was suggested that a prolonged course of exposure to cold and damp working conditions were causative, contributory, or aggravating factors in the progress of rheumatoid arthritis, he believed that in the light of present knowledge of the disease all those conclusions were untenable. He did not think that living in a damp house or sleeping in a damp bed would be positive factors. There was no high incidence of the disease among refrigeration plant workers, and fishmongers and butchers were apparently immune. It was a common disease in Spain, Switzerland, and the Arizona desert.

In his summing up[1] to the jury Lord Walker said that before they could find for Mrs. McKendrick they must be satisfied of three things: that the room was cold, damp, and ill-ventilated throughout the two and a half years she was working there; that these conditions caused or aggravated the rheumatoid arthritis from which she suffered; and that the corporation ought reasonably to have anticipated that rheumatoid arthritis was likely to occur if she was exposed to the conditions in the room.

By a majority of seven to five the jury found a verdict for Mrs. McKendrick and awarded her £2,000 damages.

[1] *Scotsman*, May 18, 1955.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending May 7 (No. 18) and corresponding week 1954.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1955					1954				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	4	0	5	0	1	9	0	3	0	1
Dysentery	862	71	393	24	4	948	107	311	3	4
Encephalitis, acute	2	0		0		5	0	0	0	
Enteric fever:										
Typhoid	3	0	0	0		2	1	1	0	0
Paratyphoid	9	0	0	0		13	0	1	0	0
Food-poisoning	155	14		1		231	102		0	
Infective enteritis or diarrhoea under 2 years				8	11				13	23
Measles*	19,492	1236	153	304	396	1,734	71	201	108	331
Meningococcal infection	29	2	14	0	1	32	2	11	1	2
Ophthalmia neonatorum	34	4	3	0		32	1	10	1	
Pneumonia†	499	23	152	13	12	506	23	183	10	2
Poliomyelitis, acute:										
Paralytic	14	1	4	0	1	15	2	2	0	0
Non-paralytic	10	0				8	1			
Puerperal fever§	274	48	11	0		244	36	16	0	
Scarlet fever	575	42	69	60	17	719	32	118	23	35
Tuberculosis:										
Respiratory	788	107	157	25		937	97	189	37	
Non-respiratory	109	9	24	8		149	8	30	4	
Whooping-cough	1,850	103	128	42	50	2,381	98	356	49	50

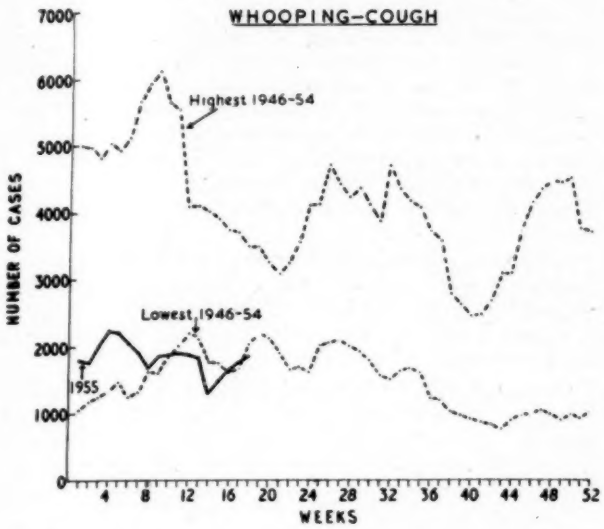
DEATHS in Great Towns	1955					1954				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	2	1	1	0	0	9	4	1	2	1
Influenza	19	1	2	1	0	11	1	1	1	1
Measles		1	0	0	0			1	0	1
Meningococcal infection		0	0				0	0		
Pneumonia	220	26	19	9	3	189	34	20	12	10
Poliomyelitis, acute	1	0			0	1	0			0
Scarlet fever		1	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	74	10	8	3	2	87	12	11	1	9
Non-respiratory		1	1	0	0			0	1	0
Whooping-cough		0	0	0	0	9	0	0	0	0
Deaths 0–1 year	201	27	28	7	11	226	28	37	9	17
Deaths (excluding stillbirths)	5,239	733	563	111	156	5,242	750	619	152	191
LIVE BIRTHS	7,596	1154	967	231	377	8,009	1227	1008	240	426
STILLBIRTHS	177	20	29			213	26	32		

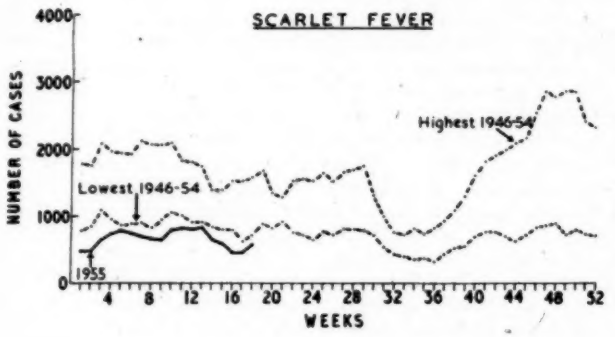
* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

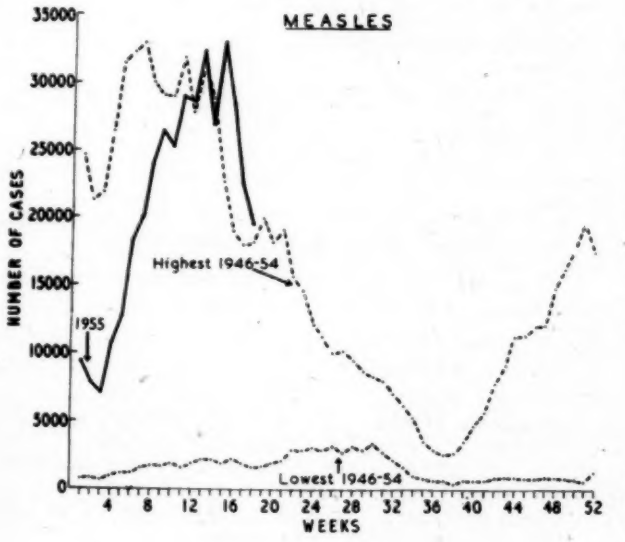
Vital Statistics

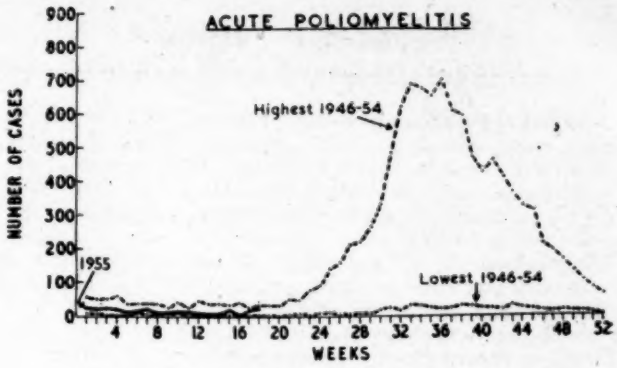
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1946–54 are shown thus ------, the figures for 1955 thus ———. Except for the curves showing notifications in 1955, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Infectious Diseases

The largest fluctuations in the notifications of infectious diseases in England and Wales during the week ending May 7 were a decrease of 3,045 for measles, from 22,537 to 19,492, and increases of 114 for scarlet fever, from 461 to 575, and 82 for whooping-cough, from 1,768 to 1,850.

The largest falls in the incidence of measles were 553 in London, from 1,789 to 1,236, 427 in Yorkshire West Riding, from 2,570 to 2,143, 424 in Warwickshire, from 2,055 to 1,631, 272 in Staffordshire, from 1,268 to 996, 258 in Southampton county, from 993 to 735, and 246 in Surrey, from 971 to 725, and the largest rises were 90 in Glamorganshire, from 603 to 693, 83 in Durham, from 719 to 802, 69 in Gloucestershire, from 410 to 479, and 64 in Middlesex, from 1,542 to 1,606. A small rise in the incidence of scarlet fever occurred in most regions, but there were no large local fluctuations. The largest rises in whooping-cough were 38 in Yorkshire West Riding, from 127 to 165, 35 in Durham, from 103 to 138, 34 in Leicestershire, from 55 to 89.

4 cases of diphtheria, 5 fewer than in the preceding week, were notified. The number of notifications was the same as in the 34th week of 1954 and is the smallest number recorded in any week. The four cases were notified in the northern cities of Kingston-upon-Hull C.B. 2, Wallasey C.B. 1, and Liverpool C.B. 1.

24 cases of acute poliomyelitis were notified, and these were 5 more for paralytic and the same for non-paralytic cases as in the preceding week. The largest returns were Lancashire 5 (Liverpool C.B. 3, Longridge U.D. 2), Middlesex 2 (Acton M.B. 2), Worcestershire 2 (Bromsgrove U.D. 2), Yorkshire West Riding 2.

The notifications of dysentery numbered 862 and were 17 fewer than in the preceding week. The largest centres of infection were Lancashire 319 (Manchester C.B. 47, Blackburn C.B. 44, Liverpool C.B. 40, Oldham C.B. 33, Blackpool C.B. 31, Salford C.B. 22, Whiston R.D. 13, Rochdale C.B. 12, Huyton-with-Roby U.D. 11), Durham 135 (Easington R.D. 26, Seaham U.D. 24, Stanley U.D. 17, South Shields C.B. 15, Felling U.D. 13, Whickham U.D. 13), London 71 (Islington 14), Surrey 44 (Woking U.D. 24), Northumberland 38 (Newburn U.D. 10), Yorkshire North Riding 36 (Middlesbrough C.B. 35), Leicestershire 31 (Leicester C.B. 22), and Yorkshire West Riding 28 (Leeds C.B. 10).

In Scotland the number of notifications of dysentery rose from 296 to 393. The largest returns were those of the cities of Glasgow 197, Dundee 61, and Edinburgh 37.

Week Ending May 14

The notifications of infectious diseases during the week included: scarlet fever 571, whooping-cough 1,805, diphtheria 9, measles 20,384, acute pneumonia 441, acute poliomyelitis 16, dysentery 1,038, paratyphoid fever 12, and typhoid fever 2.

Medical News

"Clinical Pathology in General Practice."—The 39 articles on clinical pathology which appeared originally in the *Journal* from October, 1953, to July, 1954, as part of the Refresher Course for General Practitioners are now available as a book. A leaflet describing it is inserted in this issue of the *Journal*. The book sets out to be a practical handbook on clinical pathology. It describes how best to take and preserve specimens, and discusses the value and interpretation of the various tests. It includes details of the laboratory facilities available in Britain and a full index. Written primarily for the general practitioner, this volume is likely to interest equally the hospital worker. Its cost is 21s.

Orthopaedic Accident Service.—From June 1 the Royal National Orthopaedic Hospital, Brockley Hill, Stanmore (Grimsdyke 2900), will operate a twenty-four hour accident service for the treatment of orthopaedic injuries. Facilities are available for the reception of injuries direct from the site of accident. Requests for admission or out-patient treatment should be made to the duty registrar. The service is planned to deal with major and minor injuries, and will supplement the existing special organizations of the Royal National Orthopaedic Hospital for peripheral nerve injuries, hand injuries, rehabilitation, and resettlement.

Joint Annual Meeting.—Members who have resolved to attend the Joint Annual Meeting in Canada on June 20–24 but not yet arranged to do so are asked to communicate before May 31 with the Secretary of the British Medical Association. It may not be possible after that date to reserve either a passage to the meeting or accommodation there.

Carnal Knowledge of Mental Defectives.—When a certified mentally defective patient is found to be pregnant or there is reason to think that sexual intercourse has taken place, the administrative procedure to be followed is set out in a National Health Service communication H.M. (55) 46, sent to hospital boards and committees by the Ministry of Health. The Board of Control should be informed, as before, but the following change in procedure has been made: "Following consultations with the Secretary of State for the Home Department, the Minister is of opinion that it is desirable that in future such cases should be reported to the police, not necessarily with a view to prosecution but to enable the police in consultation with the medical superintendent to decide what is the best course to take in all the circumstances." Medical superintendents are asked to send reports to the local chief constable even when the offence has been committed in another police area.

Eighth World Health Assembly.—Dr. I. MORONES PRIETO succeeded Dr. JOSEPH N. TOGBA as president of the World Health Assembly at its eighth session, which began on May 11 in Mexico City. Dr. Morones Prieto is Mexico's Minister of Health and Welfare. Dr. ANDRIJA STAMPAR, president of the Yugoslav Academy of Sciences and Arts, was awarded the Léon Bernard Foundation Prize in recognition of his "outstanding contribution and practical achievements in the field of social medicine." The prize, which consists of a medal and 1,000 Swiss francs, was presented by Dr. Morones Prieto. He stated that Dr. Stampar had introduced basic concepts of social medicine into the medical schools and health services of Yugoslavia as well as in other countries. Dr. Stampar was chairman of the Interim Commission of the World Health Organization in 1946–8 and president of the First World Health Assembly in 1948.

NAPT Travelling Fellowship.—The Scottish Branch of the National Association for the Prevention of Tuberculosis offers a travelling fellowship, valued at £250, to a doctor working in Scotland in the field of tuberculosis. Details from the Scottish Secretary, NAPT, 65, Castle Street, Edinburgh, 2. The last date for applications is July 15.

Rockefeller Foundation Grants.—Among recent grants are one of $35,000 to the University of London for research into nucleic acids by Professor J. T. RANDALL and Dr. M. H. F. WILKINS in the department of physics at King's College, and another of $45,500 (£15,000) to the London School of Hygiene and Tropical Medicine for the investigation of industrial conditions hazardous to health in a new department of occupational health. The present grant brings the total support to this school by Rockefeller funds to about $2,500,000 since 1922. Professor H. A. KREBS, Nobel Prize winner, recently of Sheffield and now professor of biochemistry at Oxford, will continue to be aided by a grant made to Sheffield University when he was there. This grant for Dr. KREBS's work is a continuation of Rockefeller Foundation support which began in 1935.

Cerebral Palsies.—A century after the publication of Little's classical descriptions of cerebral palsy a Little Committee has been formed to study the clinical features of the disease and the administrative problems of training medical and other staff for work on it. The committee consists of the following members: Dr. W. R. F. COLLIS (chairman), Mrs. EIRENE COLLIS, Dr. WILLIAM DUNHAM, Dr. L. T. HILLIARD, Sir FRANCIS WALSHE, Dr. DAVID LAWSON (secretary at Queen Mary's Hospital for Children, Carshalton, Surrey).

Paediatrician Honoured.—On May 6 at the Dewsbury General Hospital local doctors and nurses entertained Professor C. WILFRED VINING, when a plaque was unveiled to commemorate his work as paediatrician to hospitals in the district from 1930 to 1953.

Medical Patron.—Lord IVEAGH, who is to be invested as a Knight of the Garter on June 13, has been a friend of medicine all his life. As a young man at Cambridge he became interested in research and in 1900 persuaded his father to endow the Lister Institute with a gift of £250,000. He was also associated at an early stage with the work of Wright and Fleming at St. Mary's Hospital. This was the result of a meeting called by Arthur Balfour in his room at the House of Commons to discuss the treatment of influenza by inoculation. It was then decided to form a committee to further the work being done at St. Mary's, of which Rupert Guinness (as he then was) was one of the most active members. In 1921 Lord Iveagh became chairman of the Wright-Fleming Institute of Microbiology and in 1929 presented it with the sum of £40,000 to be spent on new laboratories. He also endowed a ward at the hospital. He was a lifelong friend of Sir Alexander Fleming, who lived for many years as his neighbour in Suffolk. It was on Fleming's suggestion that early in the century he installed a pollenarium on his estate at Pyrford in Surrey. Here for many years the special grasses have been grown to provide the pollen from which vaccines for the treatment of hay fever are manufactured.

Research Fellowships.—The following Beit Memorial Fellowships for Medical Research are announced:

P. C. CALDWELL, D. Phil.: to investigate the mechanism of muscular contraction in Crustacea at the Marine Biological Laboratory, Plymouth.

R.-H. CÔTÉ, D.Sc.: to investigate the chemical constitution of human blood group substances at the Lister Institute of Preventive Medicine.

Miss E. I. B. DRESEL, Ph.D.: to investigate the biosynthesis of porphyrin pigments at University College Hospital Medical School, London.

J. M. LOWENSTEIN, Ph.D.: to investigate the biosynthesis of pyrimidines in mammals at the Department of Biochemistry, Oxford.

R. WHITTAM, D.Phil.: to investigate the metabolism of adenine nucleotides in relation to the active transport of inorganic ions at the Physiological Laboratory, University of Oxford.

Orthopaedic Meeting.—On April 22–23 the President of the British Orthopaedic Association, Professor BRYAN MCFARLAND, and some twenty members attended the spring meeting of the Société Belge d'Orthopédie et de Chirurgie de l'Appareil Moteur at Brussels at the invitation of the society's president, Dr. ROBERT SŒUR.

Ulster Paediatric Society.—A meeting was held on May 7 in the Institute of Clinical Science, Belfast. A demonstration of clinical cases occupied the morning, and after lunch papers were read by Dr. O. D. FISHER, Mr. D. S. GORDON, Dr. W. A. B. CAMPBELL, and Mr. J. A. W. BINGHAM.

Rose Simmonds Memorial Fund.—The first Rose Simmonds Memorial prizes for student dietitians (see *Journal*, July 3, 1954, p. 51) were presented by Miss PAT HORNSBY-SMITH, Parliamentary Secretary to the Ministry of Health, at the annual meeting of the British Dietetic Association on April 30.

Analgesia Research.—The National Birthday Trust Fund has made a grant of £1,200 to Dr. HILDA ROBERTS, lecturer in anaesthesia at the London Postgraduate Medical School, to enable her to do full-time research. The work will be carried out in the Research Unit of Obstetric Analgesia at Hammersmith Hospital.

Honorary Degree.—When QUEEN ELIZABETH THE QUEEN MOTHER is installed as Chancellor of London University on November 24 the honorary degree of Doctor of Laws will be conferred on Viscount MALVERN OF RHODESIA (formerly Sir Godfrey Huggins).

Lady Templer Hospital, Malaya.—Dr. M. R. J. SNELLING, from the King Edward VII Sanatorium, Midhurst, has been appointed first medical superintendent of the Lady Templer Hospital for Tuberculosis at Kuala Lumpur. He will shortly be joined by a thoracic surgical team and 28 Australian nursing sisters. The hospital has 250 beds.

Dr. Scott Thomson has been appointed part-time professor of bacteriology in the University of Wales. Dr. Scott Thomson is director of the Regional Public Health Laboratory (Medical Research Council), Cardiff, and has been lecturer in bacteriology in the Medical School since 1946. He was a major in the R.A.M.C. and was bacteriologist of the penicillin research team set up by the War Office in 1943.

Dr. G. R. Hargreaves has been appointed Nuffield Professor of Psychiatry at Leeds University from October 1. Dr. Hargreaves, who qualified in 1932, was in 1948 appointed the first chief of the Mental Health Section of the World Health Organization.

Dr. K. G. Bergin, B.O.A.C.'s medical superintendent, London Airport, has been elected a Fellow of the Royal Aeronautical Society.

Dr. J. Ferguson Smith, of Glasgow, has been elected an honorary member of the German Dermatological Society "on account of his outstanding scientific services in the domain of dermatology."

Faculty of Ophthalmologists.—At the council meeting on May 13 the following were elected officers for 1955–6: President, Dr. JOHN MARSHALL. Vice-presidents, Mr. T. KEITH LYLE and Mr. J. R. WHEELER. Honorary Treasurer, Mr. A. MCKIE REID. Honorary Secretary, Mr. E. F. KING.

COMING EVENTS

"Rehabilitation of the Handicapped."—Two-day course, under joint auspices of British Council for Rehabilitation and Manchester University, at the College of Technology, Sackville Street, Manchester 1, June 6 and 7. Intended for industrialists, industrial M.O.s and nurses, personnel officers, etc. Details from British Council for Rehabilitation, Tavistock House (South), Tavistock Square, London, W.C.1.

Israeli Medical Association.—Third World Assembly in Jerusalem, Haifa, and Tel Aviv, August 10–20. Organized tour from Britain leaves London on August 8 (cost £158). Details and programme from Messrs. D. F. LONG and Co., Travel House, Mornington Crescent, London, N.W.1.

Asian-Pacific Tuberculosis Conference.—In Sydney, August 15–21, the week preceding the Australasian Medical Congress. The programme includes discussions on B.C.G. vaccination and tuberculosis control and treatment. Details from Dr. BRUCE GEDDES, Royal North Shore Hospital of Sydney, Crows Nest, New South Wales.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, May 30

EDINBURGH UNIVERSITY: FACULTY OF MEDICINE.—At Large Surgical Lecture Theatre, Edinburgh Royal Infirmary, 12 noon, Professor S. F. Haines (Minnesota, U.S.A.): Thyroid Gland in Relationship to Neuromuscular Disease.

Tuesday, May 31

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. J. E. M. Wigley: The Alopecias.

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—3 p.m., Mr. F. C. Dwyer: Lumbo-sacral Backache.

OXFORD UNIVERSITY MEDICAL SOCIETY.—At Maternity Lecture Theatre, Radcliffe Infirmary, 8.15 p.m., Professor R. J. Harrison: Origin, Development and Treatment of Human Intersexes.

ROYAL STATISTICAL SOCIETY: STUDY CIRCLE ON MEDICAL STATISTICS.—At Westminster Medical School, 5.45 p.m., annual general meeting. Three short papers: Controlled Trials in Medical Research. Dr. P. Armitage: Sequential Methods; Dr. J. Knowelden: Some Practical Problems; Dr. R. F. Wrighton: Statistical Inference.

UNIVERSITY COLLEGE LONDON: DEPARTMENT OF PHARMACOLOGY.—At Physiology Theatre, Gower Street, W.C., 5.15 p.m., Cushny Memorial Lecture by Professor G. M. Bull: Physiology of Osmotic Diuresis and its Clinical Effects.

WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY.—5 p.m., Almroth Wright Lecture by Professor A. C. Frazer: Studies on Intestinal Function in Man.

Wednesday, June 1

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. W. Riddell: Diagnosis and Treatment of Tinea Capitis.

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—3 p.m., Mr. N. F. Morris: Face and Brow Presentation.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. I. Friedmann: Pathology of the Ear.

Thursday, June 2

HONYMAN GILLESPIE LECTURE.—At University New Buildings, Edinburgh, 5 p.m., Dr. John Gillies: Induced Hypotension—A Review.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Hunterian Lecture by Professor R. Roaf: Natural History of Deformities as seen in India.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., postgraduate demonstration in neurology.

SURREY INTER-HOSPITAL PSYCHIATRIC ASSOCIATION.—At Horton Hospital, Epsom, Surrey, 8 p.m., clinical meeting. Papers by Dr. A. R. Worters: Problem of Incontinence in the Senile Psychotic; Dr. G. H. A. Chamberlain: Investigation into the Use of Acetylcholine in the Chronic Psychotic.

Friday, June 3

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., clinical demonstration by Dr. L. Forman: Disorders of Hair and Scalp.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., clinical demonstration by Dr. J. G. Scadding.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., Mr. N. Asherson: Intra-cranial Complications of Ear and Sinus Disease.

LONDON ASSOCIATION OF THE MEDICAL WOMEN'S FEDERATION.—2.30 p.m., visit to Heritage Craft School and Hospital, Chailey, Sussex.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Sir Arthur Porritt: Carcinoma of the Breast.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Theatre, 5 p.m., Dr. J. Suchet and Dr. M. W. Lloyd-Owen: Analgesia and Anaesthesia in Labour.

APPOINTMENTS

FAIRLEY, H. BARRIE, M.B., B.S., F.F.A. R.C.S., D.A., Anaesthetist, Toronto General Hospital; Clinical Assistant, University of Toronto.

HENRY, H. S. A., M.B., F.R.C.S.I., D.L.O., Part-time Consultant Ear, Nose, and Throat Surgeon to South Down and South Armagh Group of Hospitals, Northern Ireland Hospitals Authority.

MACDONALD, IAN ALISTAIR, M.D., D.P.M., Consultant Psychiatrist and Medical Superintendent, Highcroft Hall Hospital, Birmingham.

MAKEY, A. R., M.S., F.R.C.S., Part-time Assistant Surgeon, Charing Cross Hospital.

VOIGT, ETHEL MARY, M.B., B.Ch., Assistant County Medical Officer/School Medical Officer, Wiltshire County Council.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Longstaff.—On May 18, 1955, at Westwood Hospital, Beverley, East Yorks, to Peggy (formerly King-Davies), wife of Dr. John Longstaff, a daughter—Fiona Sarah.

Rose.—On April 20, 1955, at Rotorua, New Zealand, to Flora Rose (formerly Macdonald), M.B., B.S., wife of Benjamin Rose, M.R.C.P., a son—Timothy Julian.

DEATHS

Allott.—On April 29, 1955, at Besborough Heath End, Farnham, Harold Wordsworth Leach Allott, M.R.C.S., L.R.C.P., Lieutenant-Colonel, R.A.M.C., retired.

Bailey.—On April 27, 1955, at Dartmouth, Devon, Charles Henry Farley Bailey, M.R.C.S., L.R.C.P., late of Newport Pagnell, Bucks, aged 81.

Brakenridge.—On April 14, 1955, at Chew Magna, near Bristol, Francis John Brakenridge, C.M.G., M.R.C.S., L.R.C.P., D.P.H., Colonel, late R.A.M.C., retired, aged 83.

Browne.—On April 23, 1955, Hugh Derbyshire Browne, M.R.C.S., L.R.C.P., of Margam Cottage, Haywards Heath, Sussex.

Circuit.—On April 4, 1955, at Little Glemham Rectory, Woodbridge, Suffolk, Kathleen Circuit, M.R.C.S., L.R.C.P.

Clarke.—On April 27, 1955, at the Royal Naval Hospital, Chatham, Kent, Hubert Arthur Clarke, M.R.C.S., L.R.C.P., L.D.S., Surgeon Commander, R.N., retired, of Trincomalee, Pevensey Bay, Sussex.

Clarkson.—On April 15, 1955, George Aylwin Clarkson, F.R.C.S., of Oakhurst, Gander Hill, Haywards Heath, Sussex, aged 85.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Vaccination for Genital Herpes

Q.—*Could you please give me an opinion on the efficacy of vaccination therapy in a case of recurrent genital herpes? What is the best method of administering vaccination therapy, and how great is the danger of encephalitis?*

A.—I am not aware of any published series of cases of the treatment of herpes genitalis by vaccination. My own impression from treating these cases is that vaccination is less effective than in the treatment of recurrent herpes on the face. However, other treatment of herpes genitalis is so unsatisfactory that the vaccine treatment is usually indicated. The vaccination should be carried out at intervals of a fortnight to a total of six or eight inoculations.

The danger of encephalitis seems to be almost entirely confined to primary vaccination in adolescents and adults. Re-vaccination is almost free from this risk.

Gaseous Distension of the Colon

Q.—*A man of 60 complains of severe flatulence after a meal. X-ray examination shows gross gaseous distension of the colon by reason of which the stomach, which is of the "cascade" type, seems almost to be pushed up into the chest. What is the best line of treatment?*

A.—Excessive gas in the colon may displace the stomach and has a number of causes, but most cases of severe flatulence after a meal are in fact due to air swallowing, with accumulation of air in the stomach under the left diaphragm, and not in the colon. If, as in this case, it is clearly shown in the *x*-ray picture that the gas is colonic, this may be due to intestinal carbohydrate dyspepsia, provided all causes of obstruction can be ruled out.

The commonest cause of this dyspepsia is undue hurry in the passage of food through the small intestine with resulting bacterial fermentation of starch which has reached the colon undigested. There is sometimes an associated achlorhydria and often an excessive excitability of the autonomic nervous system. The treatment is to cut down drastically all starches in the diet—particularly vegetables—and to give small doses of a sedative such as phenobarbitone, ½ gr. (32 mg.) three times a day, to reduce nervous excitability, and acid. hydrochlor. dil., 15 min. (0.9 ml.), daily, with the two main meals of the day, in a glass of water.

Gas absorption in the small and large intestine may be reduced in cases of portal hypertension or heart failure, and severe meteorism may be due to a small mesenteric thrombosis.

Presumably in the case described all causes of chronic obstruction such as volvulus or peritoneal bands have been excluded, but simple chronic constipation in elderly patients, either of the "dyschezia" type or associated with diverticulitis, may sometimes lead to a considerable degree of megacolon with much gaseous distension. If this is the case a short course of colon washouts might be tried, giving these daily for four or five days to see if relief occurred. Two ounces (56 ml.) of liquid paraffin should first be run into the rectum and retained for one to three hours with the patient lying flat, after which 1 to 2 pints (0.5 to 1 litre) of warm saline should be run into the rectum under low pressure and then allowed to be evacuated.

Abdominal massage is unlikely to be of assistance, and the use of purgatives actually detrimental. Charcoal and other so-called adsorbents are almost, if not entirely, useless. Unless stool cultures show a definitely abnormal flora antiseptics or antibiotics should not be given.

Careers for Tuberculous Patients

Q.—*What principles should govern the choice of a career for a patient with tuberculosis? Training colleges will not accept active cases nor, presumably, quiescent ones. Should going to the university be postponed until the disease is arrested? Should careers involving much examination study be avoided? Should office work be avoided, as many offices are stuffy and badly ventilated? Your expert's views would be helpful.*

A.—It is possible nowadays to take a much more optimistic view of tuberculosis than formerly. In the writer's opinion, although each case must be judged on its merits, a patient with arrested tuberculosis could in general be accepted for a training college, provided he remains under supervision by a competent chest physician. Nowadays relatively few careers have to be closed to a patient just because he has had tuberculosis. The university certainly need not be postponed for any long period; in the writer's experience most students found to have pulmonary tuberculosis by mass miniature radiography are back at the university the following academic year. They are advised to have 9 to 10 hours in bed and have to forgo strenuous sports, but are quite able to undertake the normal amount of study. It follows, of course, that there is no need to forgo a career which involves examinations. Office work, with its routine hours and lack of physical exertion, is in general very suitable for the ex-tuberculous patient. At present it is wise to advise against jobs involving heavy physical effort or dusty conditions, but it may well be that even these will later be opened to suitable ex-patients. All these remarks apply, of course, only if the patient has been well and thoroughly treated, if he remains under skilled supervision, and if his disease is regarded as securely under control.

Preservation of Fibrinogen

Q.—*Solutions of fibrinogen prepared by the method of Jaques appear to become readily infected when stored at 4° C. What is the best method of preserving these solutions?*

A.—Solutions of fibrinogen cannot be stored even in the refrigerator at 4° C. for more than two or three days. The reactivity of the fibrinogen deteriorates even if the solutions are not infected. Nor, in my view, is preservation improved by freezing the solution solid at −20° C. The only satisfactory method of storage is to dry the solution by the lyophil drying method immediately the solution has been dialysed. The material can be made in quite large bulk, and suitable amounts weighed out and dissolved as required. Advice on the construction of a satisfactory freeze-drying apparatus can be obtained from any well-equipped university biochemistry laboratory.

Vaginal Pessaries in Virgins

Q.—*How does one treat a virgin who has a Trichomonas vaginalis infection? Is there not a risk of damage to the hymen if vaginal pessaries are used? I would appreciate your advice.*

A.—If the opening in the hymen is wide enough to allow swabs to be taken and the diagnosis to be made, it nearly always allows the patient to insert vaginal pessaries without injury. Even if their regular use does result in slight stretching or tearing of the hymen it does not matter so long as the patient is responsible for it herself.

In cases where the hymeneal opening is exceptionally small and when the patient is nervous, uncooperative, or lacking in self-confidence it may sometimes be necessary to get her permission (or that of her parents if she is under age) to administer a general anaesthetic with a view to vaginal examination: this will inevitably dilate or tear the hymen. It will allow the case to be properly assessed, and has the added advantage that it allows a thorough cleaning of the vagina before the start of the treatment with pessaries.

Anticoagulants in the Puerperium

Q.—*Is there any evidence that anticoagulants given to the mother for phlebothrombosis in the puerperium may be passed on to the baby through the breast milk and cause spontaneous bleeding?*

A.—Anticoagulants of the heparin group are not absorbed from the intestinal tract and are therefore harmless to the baby even if excreted in the breast milk. The dicoumarol group of anticoagulants (dicoumarol, ethyl biscoumacetate, phenylindanedione) given to the mother are excreted in breast milk and can be absorbed from the intestinal tract. There is therefore the theoretical possibility that the baby might absorb sufficient anticoagulant from the breast milk to disturb its own clotting mechanism. No case of prolonged bleeding in a baby seems yet to have been reported as a result of administering anticoagulants to the mother in the puerperium, and it is not very likely that enough anticoagulant would in practice be absorbed to increase the baby's clotting-time significantly. An injection of vitamin K (5 mg.) would rapidly restore the normal coagulation rate if this was found to be raised.

Nocturnal Epilepsy in a Boy

Q.—*What is the best drug for a boy aged 12 who suffers from nocturnal epilepsy? He began to have the fits eight months ago. Physical examination was entirely negative and x-ray examination showed nothing abnormal. He has never had an attack during the day. He was kept free from attacks with phenobarbitone, ½ gr. (32 mg.) at bedtime, until two weeks ago, when the fits began again (he was away from home at the time). Now phenobarbitone, 1 gr. (65 mg.), keeps him all right. I would welcome suggestions as to treatment.*

A.—In the treatment of epilepsy it is best to begin with a trial of whatever anticonvulsant may seem to be the most suitable, and, if it is ineffective in the dose first given, to increase this up to the limit of the patient's tolerance. If this should fail, other drugs or combinations of drugs should be tried. In the present case 1 gr. of phenobarbitone appears to be effective, and this should therefore be continued. It is important that whatever drugs may prove effective in controlling the seizures should be continued without reduction of the dose for a long period. This might reasonably be for three years after the last seizure, during which time the growth of the patient will have brought about a reduction of the dosage in relation to body weight. At the end of that time the dose might be halved, and if at the end of a further six months there had been no recurrence of seizures treatment might be stopped.

Intraperitoneal Sulphonamides in Research

Q.—*In the course of experimental work on the pathology of certain obscure diseases of animals, in particular reptiles, I want to use a sulphonamide preparation systemically, but the only satisfactory route of administration is intraperitoneal. Can you please suggest the most suitable preparation for this purpose?*

A.—It has been the general experience of experimental workers on the pharmacology of sulphonamide and allied drugs that the intraperitoneal route offers a safe and effective method of administration.

The simple sodium salt solutions are too alkaline for administration in this way, and it has been usual to use simple suspensions in saline or in 10% gum acacia of finely powdered (pestle and mortar) drug. The newer carboxymethyl cellulose preparations such as are employed in intramuscular penicillin suspension make excellent suspending agents. A site on the midline, above the bladder and avoiding the spleen, is chosen; a new *sharp* needle is the best safeguard against penetration of gut or vital tissue. The usual safeguard of withdrawing the needle a few millimetres and then withdrawing the piston before slowly injecting should be practised. Absorption of sulphonamide drugs from the peritoneum of small laboratory animals and cats and dogs is rapid, approximating more to the intravenous than to the intramuscular route. It seems likely that this would also be true of reptiles.

The wide range of acetylation of sulphonamides among animals, and the possible sequelae of crystallization of acetyl-derivatives in, for example, warm atmospheres, would have to be considered, and this might influence the choice of drug. The writer has seen no reference to acetylation in reptiles, and a cautious experimental approach to dose is suggested. A calculation based on weight (man) should first be attempted; thereafter an increased dose based on surface area should then be used. For small reptiles the latter might well be seven times the former. Sulphathiazole remains the first choice.

Prognosis in Aplastic Anaemia

Q.—*What is the longest recorded interval between onset and spontaneous recovery of the marrow in a case of aplastic anaemia? We have under our care a patient with panhaemocytopenia who, in the last four months, has had about 50 pints (28 litres) of blood. The frequent transfusions are causing great distress to the patient, and we are beginning to wonder whether further transfusion is justified. We should be very grateful for your expert's views.*

A.—The writer is unable to answer the question as to the longest recorded interval between the onset and spontaneous recovery in aplastic anaemia. In the typical "idiopathic" form of the disease in which the marrow is truly aplastic recovery is undoubtedly extremely unusual. However, patients in whom the marrow aplasia is less complete have been kept alive for several years by blood transfusions, and in the writer's opinion the patient should never be allowed to die from lack of red cells. Even if the chances of recovery are remote, who can say that an individual patient will not recover or have a worthwhile remission? Is the distress to the patient caused by the transfusions psychological, or are the transfusions technically difficult or usually accompanied by reactions? If reactions occur frequently, they might be avoided by careful selection of blood after carrying out investigations for immune iso-antibodies. Possibly, too, transfusions of washed cells might be tolerated better.

Osteo- or Rheumatoid Arthritis?

Q.—*My wife, aged 59, has recently developed painful Heberden's nodes on the terminal phalanges. She has fine crepitus in the knee-joints, but otherwise no other signs of rheumatoid arthritis. She has had salicylates and is now having phenylbutazone (1 tablet three times daily). Can you suggest any other treatment to retard the development of rheumatoid arthritis?*

A.—Painful Heberden's nodes and fine crepitus in the knee-joints are signs of early generalized osteoarthritis, a condition which is extremely common in middle-aged women and which rarely causes serious crippling. Although the affected joints are painful in the early stages, this is followed by bony enlargement which is relatively painless. A more detailed description of the clinical and radiological features of this type of arthritis was published not long ago in the *British Medical Journal* (1952, **1**, 181).

There is no evidence that this form of oesteoarthritis predisposes to the development of rheumatoid arthritis, but rheumatoid arthritis is not uncommon in the sixth decade, and the two conditions may therefore coexist. Rheumatoid arthritis should be suspected if the following features are present: (1) Constitutional illness with weight loss; (2) cool, mauve, moist extremities; (3) marked soft tissue thickening around the joints; and (4) severe morning stiffness lasting two or three hours.

When there is any doubt, *x*-ray examination of hands and feet and a differential agglutination test for rheumatoid arthritis which is now done at most of the major rheumatism centres will help to clarify the diagnosis. Slight elevation

of the sedimentation rate is not uncommon in polyarticular osteoarthritis, but marked elevation will be strongly in favour of a concomitant rheumatoid process.

In generalized osteoarthritis rest of the affected joints and local warmth give the best relief of pain. Drug therapy with salicylates, phenylbutazone, etc., is generally less effective than in other rheumatic diseases.

Stilbamidine and Trigeminal Neuralgia

Q.—*Can you give me any information on the use of stilbamidine in the treatment of trigeminal neuralgia? A patient of mine has shown me a cutting from an American newspaper on the subject, and I am anxious to know if there is any authentic basis for the idea.*

A.—Stilbamidine has been used in the treatment of leishmaniasis. One author reports that half of a group of patients examined after such treatment had developed a trigeminal neuropathy. The patients complained of hyperaesthesia, paraesthesiae, anaesthesia, and formication in various parts of the trigeminal field. The symptoms arose three months after completion of a course of treatment and in one case had persisted for two years. Examination showed a loss of light touch sensibility with preservation of pain, both deep and superficial. These facts may have led to a trial of the drug in cases of trigeminal neuralgia. However, no reports of a series of such cases so treated (and followed for an adequate period afterwards) have appeared in the literature. The neurological findings above described would suggest that the drug would not be of value. Further, the paraesthesiae which the drug induces might add to the patient's difficulties, since it is well known that sufferers cured of trigeminal neuralgia by sensory root section or alcohol injection of the semilunar ganglion may be greatly troubled by paraesthesiae.

The Elderly Husband

Q.—*A widower of 67 has recently married a woman of 35. He was worried beforehand whether he would be able to consummate the marriage successfully, and in the event he has proved impotent despite a course of testosterone propionate. Is his impotence likely to be due solely to psychological causes, solely to physical causes, or to a combination of the two? What treatment is advised?*

A.—In view of his age, it is probable that his impotence is mainly physiological, but one would like to know how long he has been a widower, whether or not there was a decline in his sexual capacity in the latter years of his previous married life, whether sexual dreams and morning erections still persist, and a great many other things. The age at which sexuality disappears differs enormously in different individuals, some men retaining their potency well into the 70's and others ceasing to take any interest in sex in the late 50's.

If lack of intercourse is causing his wife distress and some treatment has to be attempted, I would recommend the implantation of tablets of testosterone, a form of therapy more effective than testosterone given by injection. Any psychological factors present will also have to be dealt with. The outlook is not good.

Amoebiasis in Children

Q.—*In the treatment of amoebiasis in children (aged 3 years and over) what dosage of emetine is indicated? What other drugs are recommended for oral use or by enema, and in what dosage?*

A.—Children between 3 and 8 years may be given one-third of the adult dose of emetine hydrochloride, emetine bismuth iodide, or di-iodohydroxyquinoline, those aged 8 to 10 one-half, children of 10 to 14 two-thirds, and those over 14 full doses. Only acute amoebic dysentery with trophozoites of *Entamoeba histolytica* in the stool should be treated with emetine by injection. Adults should be given 1 gr. (65 mg.) daily for three to four days, and this should be followed by a full course of emetine bismuth iodide. Children are given proportionately smaller doses. If cysts of *E. histolytica* only are found, emetine bismuth iodide should be given without a preceding course of emetine hydrochloride. The adult dose of emetine bismuth iodide is 3 gr. (0.2 g.) given nightly for 10 nights. This drug may cause nausea and for this reason it should be administered in the evening and preceded by a mild hypnotic. Most patients will then sleep through the period during which nausea is most troublesome. In the unlikely event of nausea and vomiting being severe, emetine bismuth iodide should be replaced by di-iodohydroxyquinoline, the adult dose of which is 0.6 g. thrice daily for 21 days. There is no justification for giving anti-amoebic drugs by enema either to children or to adults, for it is now generally agreed that the results so obtained are not superior to those following routine treatment as here outlined.

Results of Surgery in Lumbar Disk Lesions

Q.—*What are the immediate and long-term results of operating on properly selected lumbar disk lesions? Are there any special sequelae or complications to be taken into account when advising a patient?*

A.—Where the proper indications for surgery are present skilled operative treatment of lumbar disk protrusions will in most cases bring rapid and lasting relief from symptoms. Crural pain is quickly and completely relieved in the great majority, and though low back pain persists in mild form more frequently, with proper post-operative management it is rarely severe or persistent. The long-term results in several large post-operative series of patients have been satisfactory, and the incidence of recurrent protrusion requiring a second operation has been no more than 5%.

The risks to life and function are extremely small, and where the indications for it are present—in particular when crural pain is severe and persistent—operation can be recommended with confidence.

Treatment of Black Tongue

Q.—*What is the treatment of "black tongue"?*

A.—The treatment of black tongue will depend upon the cause. If it is due to overgrowth of *Candida albicans* and allied yeasts, painting with ½% to 2% gentian violet will often lead to its rapid disappearance. When it is due to some chemical or other irritant and is associated with overgrowth of the filiform papillae, producing black hairy tongue, painting with trichloracetic acid (30% to 90%) will frequently be effective. A course of superficial *x*-ray treatment (50–75 r at weekly intervals, to a total of about 300 r) is also very effective. I have found hydrocortisone lozenges (1–2.5 mg.) locally to be effective in the few cases in which they have been tried.

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